ANNALS
OF THE
RHEUMATIC DISEASES

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The Official Journal
of the
EMPIRE RHEUMATISM COUNCIL

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Owing to war conditions and the need for economy in paper, two issues only of "Annals of the Rheumatic Diseases" will be published this year, instead of four. Subscribers' payments will be adjusted accordingly.

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EDITORIAL

THE Editors regret that war conditions have seriously hampered the production of the Annals. Some contributors have been unable to complete their work in time, while postal delays and other difficulties have also interfered with publication. Several papers are in consequence deferred till the next number, which will appear, it is hoped, towards the end of the year.

The Editors gratefully acknowledge the sympathy and assistance of their colleagues in the United States, evidence of which will be found in valuable contributions in the present issue, and others have been promised for early publication. It is felt that the Annals should provide a bond of union between the workers on the problems of rheumatism in the English-speaking countries and thus help greatly in the campaign to overcome this great scourge to humanity.

The Editors will be glad at any time to receive and consider contributions bearing on the problems of rheumatic disease.

THE PRESENT STATUS OF THE LIGUE INTERNATIONALE CONTRE LE RHUMATISME*

By RALPH PEMBERTON

President, Ligue Internationale contre le Rhumatisme

Nearly three years have elapsed since the International Congress on Rheumatic Diseases was held in London, Oxford and Bath, and nearly eight months have elapsed since the date planned for the Seventh International Congress on Rheumatic Diseases which was to have been held in the United States in New York, Philadelphia and Boston in June, 1940.

In view of the unsettled state of affairs throughout the world in general and the war actively going on between many countries, it becomes appropriate to set forth the present status of the Ligue Internationale contre le Rhumatisme. It is to be borne in mind that many countries constituting part of the membership of the Ligue are not actively engaged in war, and there would, therefore, seem to exist in these countries a tacit obligation to preserve for future use such activities and lines of affiliation as had been already inaugurated or laid down. Those countries whose potential is presumably most significant at the moment in this connection are obviously the United States in North America and the Argentine Republic in South America. There are other nations whose non-belligerent status permits of participation, but for many reasons the fullest co-operation can hardly be expected from them. It is further to be recognised that, even in countries engaged in actual warfare, observations of great value may conceivably emerge. It remains, therefore, to ascertain what, if anything, can be expected in attempting at the present juncture to further the original purposes of the Ligue.

There is importance in realising that affiliations along scientific lines have long been regarded as having a potential which can leap over barriers and are not confined by international boundary lines of any sort. This can hardly ever be expected to take place completely, least of all now, and yet there is no doubt that to a certain extent something in this direction is always operative.

* Received for publication February 10, 1941.

There are other considerations, however, which assume added significance at a time like the present, when institutions of democracy are everywhere threatened. For example, it is axiomatic that only in democratic countries can true freedom of thought be said to exist, since democracy exists, not as a regimented order, but rather as a collection or aggregation of independent thoughts and activities which, loosely welded together, constitute a whole. In this view, there is obviously value in times of stress of developing each of those units which may be reasonably regarded as contributing to such a whole. Importance of a nature other than scientific or medical must therefore attach to any movement which has reached the proportions achieved by the Ligue Internationale contre le Rhumatisme. As the war as a whole has developed, opinion everywhere has crystallised in one of two directions, favourable or unfavourable to democratic thought, and in so far as the Ligue is a child of democratic thought there can be small doubt as to the direction in which it, as an institution, must also face.

Significance must attach, therefore, in the minds of thinking persons, to the preservation of such lines of communication and of free thought as have been already created by the Ligue for its specific purposes. The extent to which the Ligue can, individually, contribute to resolving the affairs of the world to-day is, perhaps, small, but that it can, and should, contribute something to this end admits of no dispute. Certain it is, in any event, that many members of the Ligue residing in countries not actively belligerent at the moment, feel very acutely their obligations as citizens of these countries to express themselves in word and deed as forcefully as may be possible toward the furtherance of free thought and the free expression of opinion. Regarded in this light the Ligue, indeed, affords perhaps one of the best corporate opportunities which present to us. This brief communication, therefore, sets forth to the membership of the Ligue as a whole, and particularly to the membership in democratic countries, the resolve of the members in the United States to live up to the traditions which the Ligue has already imposed upon us, to plan for its future, and to plan for world-wide collaboration as soon as this becomes possible.

Another chief purpose of this letter is to state that the affiliations established in the field of rheumatic diseases, in both Great Britain and the United States, are regarded in the United States

of America as strengthened rather than weakened by the stresses put upon them. The only way in which the present hiatus can be regarded is in the light of a temporary deceleration of the work we have in hand, with the aim of greater acceleration in the not distant future. In planning to maintain present affiliations, and indeed to add to their significance, members of the Ligue, in common with the people of all democratic countries, those in bonds as well as those still free, can look with admiration at the example presented by Englishmen everywhere and from this example take up renewed determination to carry on.

The basis of function of the Ligue Internationale, so far as the United States of America is concerned, can be regarded as secure. The specific nucleus of the Ligue in this country, arising directly from the American Committee for the Control of Rheumatism which was created by the Ligue, is the American Rheumatism Association, a body of 250 close students of the subject which, in June next, will hold its eighth annual meeting. Notwithstanding the extent to which this country is now engaged in preparations for defence, a lengthy and significant programme has been prepared to which many of the leading workers in this field will contribute. Apart from this, wide interest has been aroused in this country by the American Rheumatism Association in the various phases of rheumatic disorders, and work is now proceeding from many quarters along lines parallel to the basic topic as a whole. This trend is well reflected in the annual scientific exhibits of the American Medical Association and in other exhibits and meetings of the kind. Homogeneity of thought is undoubtedly slowly arising in regard to the importance of this group of diseases and as to the way in which they should be approached from the sociologic and therapeutic standpoint. Many of the shibboleths which in the past twenty years have acted as a brake to independent thought and research have been modified or broken down. The changed viewpoint in the United States of America towards the exclusive, etiologic rôle of focal infection has given way to a wider-angled outlook which sees the problem of rheumatic diseases as the resultant of imbalance in many systems of the body. This more tolerant and broader form of inquiry can have only useful consequences.

In addition to many centres of independent study of these diseases, there have been established in the United States of America in the past few years several great foundations whose

funds and potential are directed solely or chiefly to the rheumatic field. At the University of Michigan the Rackemann Foundation has provided for a comprehensive, long-range study of arthritis, and in New York a large hospital has been built and dedicated to the treatment of, and research in, chronic diseases, arthritis being one of the three diseases selected. In Boston the Lovett and Commonwealth Foundations, with large-scale assistance from the State of Massachusetts, have inaugurated basic studies, already bearing significant results. It is much too soon to attempt to evaluate all that is being accomplished in this connection, but it is fair to state that by the time peace returns to the world, be this soon or late, the members of the American Rheumatism Association will have a full message to deliver.

It is at such a time that the postponed meeting of the Ligue Internationale contre le Rhumatisme should be held. Unusual stimulation will derive from renewing interchange of thought, and it is not too much to suppose that added impetus will also be given to those plans, which must then be formulated and executed, to bring about that stability which the world will then everywhere need.

RECENT STUDIES ON ARTHRITIS AND RHEUMATISM IN THE UNITED STATES*

By PHILIP S. HENCH

Diseases of Joints Related to Trauma

After acute trauma to a small joint, such as the wrist or ankle, the bones of the adjacent hand or foot may rarefy and notable regressive changes may occur in overlying soft tissues (muscle atrophy, vasomotor and trophic changes in skin, perhaps swelling of soft tissues). This not uncommon condition is known as "Sudeck's atrophy" or "Leriche's disease." Little is known of its underlying pathology. It is now reported that a somewhat similar series of events also may occur after trauma without fracture to large joints.[43] A violent wrench or blow to a knee occasionally may lead to a severe disabling atrophy of the local

* Received for publication April 4, 1941.

muscles, sometimes with the appearance of one or more small areas of rarefaction in the spongiosa near the joint. In some cases more extensive rarefaction of bone occurs which may extend far along one or all of the bones entering into the formation of the joint; this rarefaction involves both spongiosa and cortex. Biopsy in two such cases indicated that rarefaction was due to hypervascularisation of affected tissues, especially of cortical bone, and pain arose from functional strain on weakened bones. Recovery is favoured by physical therapy and use, not rest, of the affected parts.

Gonorrheal Arthritis

Although gonorrhea still holds first place as a cause of sick days in United States naval hospitals, within six years the annual incidence has decreased more than 90 per cent.[61] The greatest factor in producing this improvement was the realization that chemical prophylaxis was almost useless, "little more than a superfluous ritual, something like the use of a finger bowl at the conclusion of a dinner," but that rubber prophylaxis was about 100 per cent. effective. The incidence of gonorrheal arthritis is about 2 per cent. of the cases of gonorrhea in the navy. Gonococcal tenosynovitis of flexor tendons of hands may be more common than has been supposed: the gonococcus was responsible for a third of the cases of tenosynovitis in one series.[36]

Diagnosis.—The cultural method of McLeod (1934), or one of its modifications, provides the most reliable diagnostic procedure. In a study[56] of 5,391 cultures and corresponding smears in cases of possible residual gonorrhea, the cultural method uncovered five times as many positive and suspicious cases as did the smear technic. Sulfanilamide does not affect the specificity of the gonococcal complement fixation test, but in a given case of gonorrhea the reaction may sometimes remain negative because the spread of the disease has been prevented by the drug, and hence an immunologic response may be lacking.[19] Prompt reversal of the fixation test from a positive to a negative reaction can be used as a criterion of cure, but use of the test should not supersede clinical or bacteriologic evidence of cure. If fixation tests give positive reactions for more than five months, additional clinical and bacteriologic investigations are indicated. Negative fixation tests do not necessarily mean absence of gonococcal infection.

Treatment.—The literature under review contained innumerable papers on the treatment of gonorrhea with the sulfonamide drugs, but few on the treatment of gonorrheal arthritis therewith. Among a total of fifty-seven cases of gonorrheal arthritis considered in five reports[12, 18, 47, 77, 89] sulfanilamide (*p*-amino-benzene-sulfonamide) produced a prompt cure in forty-five cases (almost 90 per cent.). Infected synovial fluids were sterilized within two to seven days; despite this, significant damage to synovial membrane sometimes occurred. Usually, but not always, the local genital focus also was cured. The number of cells in the synovial fluid diminished, and fluid accumulated much less rapidly with the use of sulfanilamide than with the older remedies. Sulfanilamide did not of itself hinder the formation of immune bodies,[47] but gonococcal complement fixation tests failed to become positive in some cases of gonorrheal arthritis in which infected synovial fluids responded promptly to the sulfanilamide.[3] Best results were obtained when the level of sulfanilamide in the blood was 10 mg. per cent. or higher. This was accomplished by giving large doses of the drug at regular intervals day and night, and by keeping the fluid intake constant (2,000 c.c. daily). Under such conditions improvement should begin within forty-eight to ninety-six hours. If it does not, the condition is probably sulfanilamide-resistant, and some other form of therapy (alone or in conjunction with sulfanilamide) should be instituted.

A few reports[40] concerned the effect of fever therapy alone; " cures " were obtained in from 25 to 70 per cent. of cases; little or no relief resulted in 10 to 30 per cent.; in the rest improvement was moderate to marked. Fever sessions were usually for five to eight hours at 106° to 107° F. Failures were due to inadequate heating or to residual damage present prior to the use of hyperpyrexia.

The combined use of fever therapy with chemotherapy was found to be superior to the use of either alone. Such a combination was successful in from 90[1] to about 100 per cent.[59] of cases of gonorrhea or gonorrheal arthritis, resistant to either alone. Some physicians[59] used sulfanilamide for three or four days prior to one ten-hour session of fever. Others[27] gave 5 gm. of sulfanilamide daily for two days, then six or eight hours of fever (106·4° F.); of fourteen patients so treated eleven were cured.

Since the literature referred to appeared some physicians

have reported their belief that sulfathiazole (2-sulfanilamidothiazole) or sulfapyridine (2-sulfanilamidopyridine) is superior to sulfanilamide in the treatment of gonorrheal arthritis. But if a patient does not show notable response to the sulfonamide drug of choice within three or four days, the combination of that sulfonamide with fever therapy is recommended, rather than a trial of some other sulfonamide without fever therapy.

Tuberculous Arthritis

The incidence of tuberculous arthritis in the United States is still decreasing; in one New York hospital fusion operations on tuberculous knees were three times as frequent ten years ago as they are now.[88] Among recent cases of tuberculous arthritis, trauma preceded articular symptoms in only 37 per cent.[88] and pulmonary tuberculosis was present in only 20 per cent.[9] Of greatest value for early diagnosis are biopsy of synovial membrane and aspiration of fluid for guinea-pig tests, but both should be done as one may give a positive, the other a negative result. In 82 per cent. of 222 tuberculous knees, biopsies revealed tubercles.

Treatment.—The current tendency is to treat children conservatively for a time, but to treat adults surgically, unless an upper extremity is affected, in which circumstance the physician may temporise for a while. Statistics prove again that the disease is serious and the mortality high.[15] Operation alone will not cure the patient but may turn the tide in his favour. Some physicians[4] were optimistic, others pessimistic about results of surgical treatment for tuberculous spondylitis. Too often bony fusion is only partial, not complete, and the disease progresses. But other physicians were no less pessimistic about the results of conservative non-surgical treatment of juvenile patients; after an average of three years of conservative treatment given to forty-seven juvenile patients who had tuberculous knees, the disease was still active in every affected knee; hence, " economical resections " to produce femorotibial synostosis were recommended.[57]

Tuberculous Rheumatism.—No recent American reports on this supposed entity have appeared; it is not an accepted condition in the United States.

Syphilis of Joints: Charcot Joints

Fifteen new cases of Charcot joints were reported with a summary of data on 586 cases collected from the literature.[71] In from 5 to 10 per cent. of the cases of tabes Charcot joints develop; multiple joints are affected in a third of these cases. Joints are not always painless. Wassermann reactions may be negative on both blood and spinal fluid even when the condition unquestionably is due to tabes dorsalis. Arthrodesis is the treatment of choice, but should be done only when articular disintegration is not too far advanced. Solid fusion was obtained by this method in nineteen of twenty-four recent cases, and in forty of forty-six cases previously reported.[30, 40]

Brucellosis: Undulant (Malta) Fever

Symptoms Referable to Muscles and Joints.—In brucellosis arthralgia is common but arthritis is rare. Occasionally the articular symptoms resemble rheumatoid arthritis or rheumatic fever. Hydrarthrosis sometimes occurs.[40]

Diagnosis.—This is difficult and depends on certain laboratory tests. One test alone is of little value; data from several tests may be valuable; if agglutination, skin and opsonocytophagic tests all give positive reactions, the evidence is almost specific.[11] A positive test by even one method occurs ten times as often in cases of brucellosis as among normal persons; positive reactions to two or more different tests occur seventy times as often among patients who have symptoms compatible with brucellosis as among controls. But it is discouraging to find such tests negative "when they should be positive."

Treatment.—A few recent cures were considered the result of specific polyvalent serum, brucellin, or fever therapy,[40] but sulfanilamide is being used more widely than other remedies. Thirty reports on this therapy were summarised;[7] results were "most encouraging." Treatment with sulfanilamide resulted in "cures" in sixty-eight (92 per cent.) and in failures in six (8 per cent.) of seventy-four cases; relapses occurred after recovery in fourteen cases (about 20 per cent.). Failures and relapses were mostly from under-treatment. Recoveries were rapid; symptoms left within two to twelve days. Recommended dosage was about $\frac{1}{2}$ grain (0·032 gm.) per pound (0·5 kg.)

of body weight per twenty-four hours, divided into six doses and continued for from three to four days after subsidence of fever (example: for a man weighing 150 pounds (68 kg.), 4 to 6 gm. or 60 to 90 grains daily); maximal dosage was 6 gm. in twenty-four hours. Some physicians were disappointed with the results of sulfanilamide; temporary improvement sometimes was followed by recurrences, and in some cases the bacteremia was affected but not the clinical picture.[10, 40]

Articular Diseases Caused by Pneumococci, Meningococci, or Hemolytic Streptococci

With the advent of highly effective chemotherapy against pneumococci, meningococci and hemolytic streptococci, articular disease, resulting from these organisms, is diminishing almost to the vanishing point. In the literature under review for this report no cases of pneumococcal or meningococcal arthritis and only one of arthritis from hemolytic streptococci were reported; in the latter case complete articular function was restored following use of sulfanilamide.[76]

Arthritis with Lymphogranuloma Venereum

Arthritis may occur with lymphogranuloma venereum as noted by Hellerstrom (1929) and by Frei (1938). The articular and osseous changes were[22, 90] considered in two recent reports. The arthritis pursues a variable course, but is usually chronic with a marked tendency to relapse. Intermittent hydrarthrosis may occur. Occasionally joints are acutely swollen, painful and tender. The arthritis is usually polyarticular and tends to affect knees, ankles and wrists. It persists for weeks or months. According to some physicians changes in bones (necrosis) and joints are apparent in roentgenograms, but in other cases[22] there was no obvious destruction of bone or cartilage, and roentgenograms revealed only periarticular swelling and intra-articular effusions. The synovial fluid varied considerably in character, but was not purulent. Cultures of synovial fluid on common bacteriologic media were sterile, but in all cases the Frei reactions were positive.

Arthritis with Haverhill (Rat-Bite) Fever

There are presumably two types of rat-bite fever: (1) Sodoku or Japanese rat-bite caused by a spirochete, the *Spirillum minus;* and (2) that caused by the *Streptobacillus moniliformis* or *Haverhillia multiformis.* Evidence is accumulating that Haverhill fever is the same as the second type of rat-bite fever. Clinically Haverhill fever and the second type of rat-bite fever resemble each other closely, and the etiologic agent appears to be the same. A complete clinical account of Haverhill fever (erythema arthriticum epidemicum) was given; thirteen reported cases were reviewed and one was added.[25]

Rheumatic Fever

Clinical Data.—In the United States there are probably 1,000,000 persons who have rheumatic carditis; the disease causes 40,000 deaths annually.[38] A study of the families of ninety-six rheumatic children and of thirty-three non-rheumatic children (controls) in Baltimore supported the belief that heredity predisposes to rheumatic fever; a family history of rheumatic fever was obtained about four times as often for the rheumatic children as for the controls.[28] New groups of rheumatic cases were reported—1,068 in one group,[31] 122 in another.[62] Differentiation between the rheumatic and non-rheumatic "growing pains" of children was given: non-rheumatic pains tend to appear at the day's end, are in muscles of legs and thighs rather than in joints, seldom involve the upper extremities, and are not associated with other signs of rheumatic activity or with abnormal sedimentation rates, leukocyte counts, or anæmia. They usually represent muscle fatigue of overactive children.[40] The abdominal pain which is a common manifestation of juvenile rheumatism usually is not associated with nausea, vomiting, diarrhœa or constipation, but occasionally simulates appendicitis or peritonitis,[84] and has led to error in diagnosis, and to appendectomy.

Laboratory Data.—Results of the formol-gel reactions were found to parallel generally those of sedimentation rates, but some physicians[6] stated that formol-gel reactions were positive in rheumatic fever only in the presence of carditis. If this observation is confirmed, the test would afford information of considerable clinical importance. In the absence of a specific

test for rheumatic fever the sedimentation rate of erythrocytes affords the most delicate index of rheumatic activity.

Cause, Prognosis, End Results.—A follow-up study, made on 1,000 rheumatic children seen between 1921 and 1936, revealed that by 1936, 239 patients were dead, 744 were living, and 17 could not be traced.[5] Of the 744 living, 605 (81 per cent.) had no physical limitations (312 had no clinical evidence of cardiac damage), 118 (16 per cent.) had slight to moderate limitation, and 21 (3 per cent.) had great limitation of cardiac reserve.

Ætiology.—It is agreed that infections, especially hemolytic streptococcal infections of the upper respiratory tract, commonly initiate rheumatic attacks, but it is not agreed that such infections are "specific" provocatives. Among 749 patients, respiratory infections preceded 58 per cent. of the first attacks of rheumatic fever; in the rest the initial attacks were apparently "spontaneous."[44] No new data to support the theories of bacterial allergy or vitamin deficiency appeared. "Pleuropneumonia-like micro-organisms" were reported[82] to have been recovered from the articular exudate of a patient with rheumatic fever, and from chorio-allantoic membranes inoculated with rheumatic exudates, and from "pneumonic lungs" of similarly inoculated mice, but later it was admitted that the "organisms" were either artefacts or micro-organisms recovered from the inoculated mice, and were not related to rheumatic fever.[40]

Treatment.—Sulfanilamide is not beneficial, but may be actually harmful in cases of active rheumatic fever or when given during the "silent period" after the onset of a precipitating sore throat.[17] Some physicians[2, 73] regarded fever therapy as beneficial, not only in cases of rheumatic chorea and polyarthritis, but also in cases of rheumatic carditis. Such therapy presumably lessened the number of recurrences of rheumatic fever and lowered the extent of cardiac damage. Other physicians[23] disagreed; hence the use of fever therapy for rheumatic manifestations other than chorea should be considered experimental.

Prophylaxis.—Although sulfanilamide is valueless in the treatment of active rheumatic fever, it appears to be most effective in the prevention of the hemolytic streptococcal infections of the throat which so commonly provoke rheumatic recurrences. Eighty children who had inactive or quiescent rheumatic fever each received 2 to 3 gm. of the drug daily for four to eight months; of these eighty children seventy-nine

escaped hemolytic streptococcal infections and rheumatic recurrences; only one child had a respiratory infection followed by a vague illness, which may have been atypical rheumatic fever.[17] Another group of thirty juvenile and adult rheumatic patients each received 15 to 20 grains (1 to 1·3 gm.) of sulfanilamide daily for seven months during each of two winters; among them no rheumatic attacks developed, but four of thirty control rheumatic patients, not given the drug, suffered from five major rheumatic attacks.[86] If these findings can be generally corroborated, the importance of these studies can scarcely be exaggerated.

Rheumatoid (Atrophic) Arthritis

Clinical Data.—A clinical analysis of 267 new cases was reported; in some of the cases 10 to 50 per cent. of the original body weight was lost within a few months.[58] Another example of the remarkable ameliorating effect of hepatitis with jaundice was reported.[51] A patient who had rheumatoid arthritis developed jaundice from cinchophen: "From the very onset of his jaundice he was completely free of the pains in his knee-joints with which he had suffered persistently over a period of ten years." Within six weeks the jaundice disappeared; then the pains in the joints returned. A somewhat similar effect was noted in five cases of cinchophen toxicity and urticaria without jaundice.[63] With the onset of the urticaria in three cases, or just after its disappearance in two cases, there was marked diminution of articular pain, tenderness, swelling and stiffness. Relief was complete in three cases, almost complete in two cases, and lasted from six weeks to five months. Thus it would appear that actual hyperbilirubinemia is not a necessary feature of this phenomenon.

Iritis develops in about 2·5 to 4·5 per cent. of cases of rheumatoid arthritis.[4]

Laboratory Data.—A moderate hypochromic anæmia and leukopenia are characteristic of this disease, but during exacerbations leukocyte counts may rise to from 9,000 to 13,000 cells per cubic millimeter of blood, and occasionally higher.[58] The concentration of serum protein is normal; values for serum albumin are normal or slightly subnormal; those for serum globulin are normal or somewhat elevated; the albumin-globulin ratio is often reduced.[64, 70] It was suggested that these data

may indicate hepatic dysfunction.[64] Regardless of the severity of the disease or the age of the patient concentrations of serum phosphatase were found to be essentially normal;[7] therefore, if a patient with rheumatoid arthritis presents an elevated value for serum phosphatase some coincident bone disease—for example, a malignant lesion or osteitis—should be suspected.

Ætiology.—No new data of significance were reported to support or refute the theory of infection or that of bacterial allergy.[40] Using the plethysmograph as a "more accurate method" for measuring circulation in fingers than skin thermometers, physicians[29] found no consistent vascular reactions or alterations in rheumatoid arthritis; circulation was diminished in some cases, increased or normal in others. Despite the current (but waning) interest in sulfur therapy no significant or characteristic alterations in sulfur metabolism were noted in this disease.[40] Patients who have rheumatoid arthritis generally have subnormal values for vitamin C in serum and seem to require large amounts of the vitamin.[35, 72] Until methods for studying the intermediate metabolism of vitamin C are available, the abnormalities observed cannot be interpreted finally. There is a growing belief that the liver plays a rôle in the production of rheumatoid arthritis,[64] but the data on liver function in this disease are so far impossible to interpret. Evidence was presented to suggest that environmental stress (poverty, grief, family worry) bears more than a chance relationship to the onset and exacerbations of rheumatoid arthritis.[16] Psychotics, however, are relatively immune to arthritis.[34]

Treatment.—The value of removing infected foci remains debatable, but American physicians agree generally, if unenthusiastically, that patients with rheumatoid arthritis who have infected foci are in a "less fortunate position" than those who have arthritis alone; hence genuine foci of sepsis should be removed. Most American physicians also will agree with the remark of a British colleague[85] regarding vaccines, "in the present state of our knowledge of the ætiology of rheumatism in general, and of rheumatoid arthritis in particular, the use of vaccines cannot either be endorsed or rejected." A few physicians still exhibit intemperate enthusiasm for such remedies as bee venom and chaulmoogra oil, but these remedies are chiefly in the discard.[40] No effective antirheumatic diet or vitamin has been discovered, but diets rich in vitamins are indicated on general grounds.

Physicians who consider the use of massive doses of vitamin D of little value in rheumatoid arthritis are now more numerous than the protagonists of this remedy.[40] Sulfur therapy was again damned with faint praise: its day is about done.

Chrysotherapy has been under investigation in the United States for only about four years. Three reports thereon recently appeared. Of one group of fifty-three patients with rheumatoid arthritis, given myochrysine, only 6 per cent. were cured, 34 per cent. were improved markedly, 25 per cent. were moderately improved; the rest were not benefited appreciably.[48] In fifty other cases gold sodium thiosulphate was employed; results were "poor" in 52 per cent., "fair" in 36 per cent., "good" in 10 per cent., and in only 2 per cent. was "cure" effected.[75] Another group of eighty patients received gold thiosulphate or aurocein; 17 per cent. were not improved, 39 per cent. were moderately improved, 44 per cent. were markedly improved, none were cured.[68] Ankylosing spondylitis was less affected than rheumatoid arthritis. From these reports it will be seen that American results have been consistently less striking than those reported from abroad, either because of greater conservatism in the appraisal of the former, or because of the tendency in the United States to use gold in fewer early and more late, resistant cases, or to use smaller, less toxic doses. The maximal individual doses in the cases in the groups noted were 50 mg. in one group, 100 mg. in the other two; courses consisted of a total of 1 gm. in two groups, 2 gm. in one. Toxic reactions occurred in 15, 49 and 63 per cent. of the cases in these three groups. They were generally mild, but occasionally severe; none were fatal, but exfoliative dermatitis, agranulocytosis and œdema of the glottis necessitating tracheotomy were noted. The mode of action of gold was not determined. It was noted that the reticulo-endothelial cells of synovial membranes in normal animals retained little gold, but in infected animals and in cases of synovial effusion with rheumatoid arthritis the synovial cells retained much gold.[50] It can be concluded that American physicians are not as enthusiastic about chrysotherapy as are their British and European colleagues. Some physicians[68] considered it superior to any other available remedy, but still not the ideal one, since it will not always stop the disease even in early cases. Others[75] considered it "too dangerous for general use," and only suitable

for patients unrelieved by older remedies. Others[48] concluded that it is not a safe procedure but is worth the risk.

Results from iontophoresis with choline and histamine preparations, from doses of bile salts, roentgen therapy and artificial fever therapy continue to be unimpressive.

A new type of arthroplasty has captured the interest of American orthopedists and rheumatologists; it involves the insertion of vitalium moulds over reconstructed femoral heads in cases of destructive and ankylosing arthritis of hip-joints.[74] Experience to date with this procedure indicates that, under the protection of the inert mould of "neutral" metal, highly developed hyaline cartilage re-forms in association with a newly formed capsule of dense fibrous tissue with a true synovial lining. The mould need not be removed. A final appraisal of the procedure cannot be made yet, but results are distinctly encouraging so far.[41]

Primary Osteo-Arthritis

Clinical Data.—An analysis of 466 cases was reported;[58] in this group Heberden's nodes affected women nine times as often as men. Although primary osteo-arthritis usually only affects persons more than forty years old, premature cases are not infrequent, and in 30 per cent. of the cases in this series the disease developed before the patient was forty years of age; twelve patients were less than twenty years of age.

Laboratory Data.—Serum phosphatase is normal in hypertrophic arthritis but is elevated in certain bone diseases such as malignancy and Paget's disease.[78] Most patients who have hypertrophic arthritis are in the cancer-bearing age. If the question of coincidental malignant disease arises in a case of obvious hypertrophic arthritis, the presence of an elevated serum phosphatase would suggest that the patient is suffering from more than his primary osteo-arthritis.

Ætiology.—No new data of striking significance have appeared. The theory that osteo-arthritis results from degeneration secondary to arteriosclerosis of articular vessels was not supported by the results of a study which showed no relationship between vascular changes in synovial vessels and the articular alterations present.[49]

Treatment.—Recent reports were rather nihilistic, serving to do away with therapeutic débris rather than proposing new

remedies.[40] "Vitamins are harmless and may be used if the spiritual support of pills is required."[58] Few physicians were impressed with the results from injections of sulfur, vitamins, vaccines, bee venom, chaulmoogra oil or gold, or from roentgen therapy, fever therapy or iontophoresis with vasodilating drugs. Local injections of, and regional anæsthesia with, procaine were recommended.[79] In general synovectomy is not indicated since the synovial membrane is rarely affected.[81]

Osteo-Arthritis Secondary to Aseptic Necrosis of Bone

Seven cases of aseptic necrosis of bone resulting in osteo-arthritis of adjacent joints were reported.[46] In four cases massive infarction of bone resulted from caisson disease, in three cases no cause was found. Necrosis of bone was produced by injury of tissues from release of nitrogen bubbles produced by too rapid decompression. When necrotic bone was situated at the epiphyses and bordered on joints, varying amounts of articular collapse occurred. Cartilage overlying the involved parts broke down and was replaced by fibro-cartilage; a more or less extensive secondary osteo-arthritis resulted. Attempts to produce such lesions in dogs by air emboli were unsuccessful.

Backache and Sciatica

A hitherto unreported type of backache was described.[54] This consisted of a localised painful condition between two or more spinous processes; pain was aggravated by flexion and not relieved by heat and massage. Superficial tenderness was present and roentgenographic, neurologic and orthopædic examinations gave negative results. Pain was due to chronic localised inflammation of the interspinal ligaments; degenerative and inflammatory changes were present in the resected ligament. Another "new syndrome" was described and variously called "the dorsolumbar syndrome,"[45] "first lumbar nerve neuralgia,"[83] or "causalgia of the twelfth dorsal and first lumbar nerves."[42] Present in some cases were unilateral pain over the lower part of the back, iliac crest and midlumbar region with hyperesthesia of skin supplied by the affected nerves, and also abdominal pain and tenderness of variable severity; in other cases backache was minimal and abdominal symptoms were "intractable"; the latter led to useless abdominal operations. Pain was relieved by peri-

neural injections or by paravertebral sympathetic block with procaine.

Rupture of the intervertebral disks is currently a favourite subject; the literature under review contained more than thirty reports thereon. Some were especially informative.[8, 20, 21, 26, 53] The clinical features in more than 600 cases in which protruded disks were proved at operation to be the cause of low back pain, generally with sciatica, were reported. The features were described in my previous report to this journal.[39] For diagnosis, myelography with air was considered less dangerous, but less satisfactory, than myelography with lipiodol. In summary, patients who have recurring low back pain and sciatica (with or without a definite history of trauma), exaggerated spinal flexion or torsion, a positive Kernig or Lasègue sign, diminished Achilles reflexes and a value for protein in the spinal fluid of more than 40 mg. per 100 c.c., should be suspected of having protruded disk, and myelograms should be made after injection of air or lipiodol. Facetectomy alone was inadequate; laminectomy and removal of the protruded disk and the hypertrophied ligamenta flava so often present relieved the great majority of patients so treated. But laminectomy should not be done until conservative therapy (rest in bed, heat, traction) has failed and the sciatica has become recurrent.

Spondylitis

Spondylitis Ankylopoietica.—Data on 106 cases were reported.[80] The usual treatment (hyperextension in bed, use of plaster half-shells, physical therapy, corrective exercises, then braces) gave results which were unsatisfactory to one physician who devised a superior plan: preliminary correction of spinal deformity by hyperextension in bed for two weeks, then the application of a plaster jacket which was left on for weeks, to be replaced by new ones as posture improved. Reported results indicated rapid relief of muscle spasm and pain, marked improvement in sleeping despite the jacket, prevention of further spinal deformities, improved posture and position of spine and chest, retardation of vertebral bridging and prevention of progressive involvement of the hips.[80]

Spondylitis Osteo-Arthritica.—The importance of industrial trauma as a provoking and aggravating factor of spondylitis osteo-arthritica was stressed. When a worker more than forty

years old, who has symptomless, perhaps unsuspected spondylitis osteo-arthritica falls down and hurts his back, the cost to his employer is likely to be about $3,000.[60] Such cases are costly to industry, but industry must absorb the cost, for routine roentgenograms of elderly workmen are not worth the cost, and if done would result in placing many on the "employment junk heap."

Gout and Gouty Arthritis

Clinical Data.—A diet high in fat, low in carbohydrates and protein, provoked attacks of gouty acute arthritis in five cases of gout nine out of the ten times it was used.[52] Another physician, however, could not provoke attacks thereby in four cases and regarded this provocative test as unreliable.[40] A case of gout producing ankylosis in many joints was reported.[13]

Ætiology.—An interesting attempt was made[32] to associate gouty attacks with interference of the function of renal nerves. Cinchophen was found to increase the excretion of uric acid of intact animals but not of animals with denervated kidneys. Ergotamine in appropriate doses blocks sympathetic impulses to the kidney. When given in a case of gout, ergotamine produced a mild attack of gouty arthritis with diuresis of chlorides and reduction in excretion of uric acid. Thus interference with impulses through renal nerves produces effects similar to those in gout.

Treatment.—No significant additions to orthodox treatment were reported. The newer studies on the physiologic effects of colchicine on cell mitosis in animal tissues have not as yet afforded an explanation of the dramatic efficacy of colchicine in acute gouty arthritis.

Uric Acid Problem.—A new method for estimating the "true uric acid concentration" of blood by means of uricase was described.[6] Normal human blood contained an average of 3 mg. per cent. of uric acid by older methods but only 2 mg. per cent. by the "uricase method": approximately a third of the colour produced was considered due to substances other than uric acid. The effect of certain polyhydric alcohols and sugars on excretion of uric acid was studied:[32] sorbitol, given intravenously, notably increased the urinary uric acid of dogs. The effect of cinchophen on the excretion of uric acid of normal dogs was compared with that of dogs with unilateral denervation of a kidney;[33] ureters of

the dogs were first exteriorised. Cinchophen decreased the urinary volume both from the normal and from denervated kidneys and increased the excretion of uric acid by normal kidneys. After denervation of one kidney cinchophen no longer increased the excretion of uric acid from either kidney. Thus unilateral denervation produced effects similar to bilateral denervation. The coincident administration of ergotamine and cinchophen acted like denervation.

Psoriatic Arthritis

" True psoriatic arthritis " affects about 1 per cent. of patients who have cutaneous psoriasis, according to one writer.[24] Psoriatic arthritis was defined as " a form of atrophic (rheumatoid) arthritis associated with psoriasis and exhibiting a reasonable amount of synchronous activity, as evidenced by remissions and relapses, in the articular and cutaneous manifestations."[87] The characteristics in twenty-two " typical cases " were described:[24] the skin lesion appeared at an average of 6·6 years before joints became involved. Almost any joint was affected, but hands, knees and feet were affected most often. In most cases nails of fingers and toes were affected. Psoriasis frequently disappears during pregnancy.[55] In the cases observed lesions usually began to disappear at the end of the first trimester and the disease steadily improved during the rest of pregnancy. Whatever the effect of the first pregnancy on the psoriasis succeeding pregnancies produced a similar effect. Unfortunately these studies did not include comments on the effect of pregnancy on the psoriatic arthritis.

Arthritis with Periarteritis Nodosa

Arthritis and muscle pains may be associated with periarteritis nodosa; hence rheumatologists should become familiar with it. The disease is so pleomorphic in its manifestations that in most cases diagnosis is not made except on post-mortem examination. A synopsis of the subject appeared.[37] In 27 per cent. of 101 cases of periarteritis nodosa reported in the literature arthritis occurred. Unfortunately the characteristics of the arthritis were not described.

Articular Physiology

Theories on the origin and nature of a synovial fluid were reviewed.[65] It was concluded that normal synovial fluid, in cows at least, is a dialysate of blood plasma to which is added mucin of unknown origin.

Experimental Arthritis

A chronic migratory and progressive proliferative polyarthritis resembling somewhat human rheumatoid arthritis was produced consistently[67] in mice by injections of a filterable pleuropneumonia-like organism isolated from the brain of a normal mouse. No tissues but joints seemed affected. A second strain of the organism produced a disease more like rheumatic fever. Similar organisms could not be found in cases of rheumatoid arthritis or rheumatic fever.[40]

Various types of streptococcal arthritis were produced experimentally,[14, 66] but the arthritis, although somewhat similar to human rheumatoid arthritis, could not be said to have been of the human type.

Campaign against Rheumatism

British physicians have repeatedly called attention to the inadequacy of hospital facilities for British arthritics. The same difficulty exists in the United States, where most hospitals are "geared" financially and psychologically for the care of acute illnesses and injuries only, and have little room for, and less interest in, cases of chronic arthritis. Even our largest city and county hospitals can accept arthritis only for short examinations or brief periods of treatment. But, unlike their British colleagues, American physicians as a group have not adopted the view that the study and treatment of chronic rheumatic diseases is the business of the nation or of the body politic, and is one that can no longer be left entirely to voluntary effort. Therefore the campaign against rheumatism in the United States is proceeding along rather different lines from the campaign in the British Empire. American physicians continue to be more interested in clinical investigations, or what might be called the scientific aspects, rather than in the broad sociologic and epidemiologic aspects, of the rheumatic diseases. American physicians still are committed

to the idea that the solution of the problem of rheumatism and chronic arthritis will come, perhaps in the not too distant future, as a result of the work of some brilliant, hard-working physician or small team of clinical investigators working away in an adequately equipped hospital or clinic.

To date, therefore, the American Rheumatism Association has not sponsored any sociologic investigations or surveys on the incidence and contributing causes of rheumatic diseases. It has continued to sponsor the formation of an increasing number of rheumatism clinics and small-study groups in various cities, to encourage individual research, and to create a forum for the prompt and critical appraisal of such research at the annual meetings of the Association. In view of the splendid results which have been accomplished by civic and national efforts against the scourge of tuberculosis, it would seem obvious that much good could be done by enlisting the same civic and national interests against the much greater scourge of rheumatism. Convinced of this, the executive council of the American Rheumatism Association is fostering the formation of groups of interested laymen and welcoming them as associate (lay) members of the organisation. In furthering this movement the sociologic studies of British workers have been found most useful as "ammunition." Thus the work in the United States and that in Great Britain have complemented each other in a very useful way.

Preoccupied with the problems of war, British rheumatologists may find it difficult to realise that to date (March, 1941) American medicine has been but slightly affected by the war. But more serious tasks are now confronting it, and if, despite them, the campaign against rheumatism can be continued with as much zeal as that evidenced by the latest (Fourth) Report of the British Empire Rheumatism Council, American medicine will be doing well indeed.

REFERENCES

1. Ballenger, E. G., Elder, O. F., McDonald, H. P., and Coleman, R. C. (1939): *Urol. and Cutan. Rev.*, xliii. 441-443.
2. Bauer, E. L. (1939): *Amer. Journ. Med Sci.*, cxcviii. 224-229
3. Bauer, Walter, and Coggeshall, H. C. (1939): *Med. Clin. North America*, xxiii. 1173-1191.
4. Berens, Conrad, Angevine, D. M., Guy, Loren, and Rothbard, Sidney (1938): *Amer. Journ. Ophth.*, xxi. 1315-1327.
5. Bland, E. F., and Jones, T. D. (1937): *Trans. Amer. Climat. and Clin. Assoc.*, lii. 85-97; *Journ. Amer. Med. Assoc.*, 1939, cxiii. 1380-1382.

6. Blauch, Mary B., and Koch, F. C. (1939): *Journ. Biol. Chem.*, cxxx. 443-454.
7. Blumgart, H. L., and Gilligan, Dorothy R. (1939): *Med. Clin. North America*, xxiii. 1193-1203.
8. Bradford, F. K., and Spurling, R. G. (1939): *Surg., Gynec. and Obst.*, lxix. 446-459.
9. Breck, L. W., and Basom, W. C. (1939): *Med. Rec.*, cl. 361-363.
10. Bynum, W. T. (1939): *Journ Amer. Med. Assoc.*, cxii. 835-836.
11. Calder, R. M. (1939): *South. Med. Journ.*, xxxii. 451-460.
12. Caldwell, G. A. (1939): *Tri-State Med. Journ.*, xii. 2358-2360.
13. Case Records of the Massachusetts General Hospital (1939): *New England Journ. Med.*, ccxx. 670-674.
14. Cecil, R. L., Angevine, D. M., and Rothbard, Sidney (1939): *Amer. Journ. Med. Sci.*, cxcviii. 463-475.
15. Cleveland, Mather (1939): *Journ. Bone and Joint Surg.*, xxi. 607-618.
16. Cobb, Stanley, Bauer, Walter, and Whiting, Isabel (1939): *Journ. Amer. Med. Assoc.*, cxiii. 668-670.
17. Coburn, A. F., and Moore, Lucile V. (1939): *Journ. Clin. Investigation*, xviii. 147-155.
18. Coggeshall, H. C., and Bauer, Walter (1939): *New England Journ. Med.*, ccxx. 85-103.
19. Cohn, Alfred (1939): *Amer. Journ. Syph., Gonor. and Ven. Dis.*, xxiii. 461-476.
20. Craig, W. McK. (1939): *Amer. Journ. Surg.* (N.S.), xlv. 499-506.
21. Craig, W. McK., and Walsh, M. N. (1939): *Minnesota Med.*, xxii. 511-517.
22. Dawson, M. H., and Boots, R. H. (1939): *Journ. Amer. Med. Assoc.*, cxiii. 1162-1163.
23. Elghammer, H. W. (1939): *Illinois Med. Journ.*, lxxvi. 527-530.
24. Epstein, Ervin (1939): *Arch. Dermat. and Syph.*, xl. 547-559.
25. Farrell, Elliston, Lordi, G. H., and Vogel, Joseph (1939): *Arch. Int. Med.*, lxiv. 1-14.
26. Fincher, E. F. (1939): *Ann. Surg.*, cix. 1028-1033.
27. Finkelstein, William (1938): *Arch. Phys. Therapy*, xix. 748-752, 762.
28. Gauld, R. L., Ciocco, Antonio, and Read, Frances, E. M. (1939): *Journ. Clin. Investigation*, xviii. 213-217.
29. Ghormley, J. W., and Silverglade, Alexander (1939): *New York State Journ. Med.*, xxxix. 1489-1497.
30. Giannestras, N. J. (1939): *Journ. Med.*, xx. 392-395.
31. Gibson, Stanley (1939): *Illinois Med. Journ.*, lxxvi. 530-536.
32. Grabfield, G. P. (1939): *Int. Clin.* (S. 2), i. 93-97; *Trans. Assoc. Amer. Physicians*, liv. 91-93.
33. Grabfield, G. P., and Swanson, D. (1939): *Journ. Pharmacol. and Exper. Therap.*, lxvi. 60-65.
34. Gregg, Donald (1939): *Amer. Journ. Psychiat.*, xcv. 853-858.
35. Hall, M. G., Darling, R. C., and Taylor, F. H. L. (1939): *Ann. Int. Med.*, xiii. 415-423.
36. Hamlin, Edward, Jr., and Sarris, S. P. (1939): *New England Journ. Med.*, ccxxi., 228-231.
37. Harris, A. W., Lynch, G. W., and O'Hare, J. P. (1939): *Arch. Int. Med.*, lxiii. 1163-1182.

38. HEDLEY, O. F. (1939): *Proc. Assoc. Life Insur. Med. Dir. America*, xxv. 163-201.
39. HENCH, P. S. (1940): *Ann. Rheumat. Dis.*, ii. 19-40.
40. HENCH, P. S. (1941): *Ann. Int. Med.*, xiv. 1838-1848 (second part to appear in March issue).
41. HOPKINS, H. H., AND ZUCK, F. N. (1938): *Med. Bull. Vet. Admin.*, xv. 1-2; 1939, xv. 217.
42. HUDSON, O. C., AND HETTESHEIMER, C. A. (1939): *Med. Times, New York*, lxvii. 211-214.
43. JAFFE, H. L. (1939): *Radiology*, xxxiii. 305-311.
44. JONES, T. D., AND MOTE, J. R. (1939): *Journ. Amer. Med. Assoc.*, cxiii. 898-902.
45. JUDOVICH, B. D., AND BATES, WILLIAM (1939): *Indust. Med.*, viii. 160-165.
46. KAHLSTROM, S. C., BURTON, C. C., AND PHEMISTER, D. B. (1939): *Surg., Gynec. and Obst.*, lxviii. 129-146, 631-641.
47. KEEFER, C. S., AND RANTZ, L. A. (1939): *Amer. Journ. Med. Sci.*, cxcvii. 168-181.
48. KEY, J. A., ROSENFELD, HERMAN, AND TJOFLAT, O. E. (1939): *Journ. Bone and Joint Surg.*, xxi. 339-345.
49. KLING, D. H. (1939): *Amer. Journ. Med. Sci.*, cxcvii. 358-369.
50. KLING, D. H., SASHIN, DAVID, AND SPANBOCK, JOSEPH (1939): *Journ. Lab. and Clin. Med.* xxiv. 1241-1245.
51. LICHTMAN, S. S. (1939): *Journ. Mt. Sinai Hosp.*, vi. 199-202.
52. LOCKIE, L. M. (1939): *Ann. Int. Med.*, xiii. 755-760.
53. LOVE, J. G. (1939): *S. Clin. North America*, xix. 943-953; *Journ. Amer. Med. Assoc.*, cxiii. 2029-2034.
54. MACEY, H. B. (1939): *Surg. Gynec. and Obst.*, lxix. 108-109.
55. MADDEN, J. F. (1939): *Minnesota Med.*, xxii. 381-385.
56. MALCOLM, MABEL M., AND DOLMAN, C. E. (1939): *Canad. Pub. Health Journ.*, xxx. 252-259.
57. MCKEEVER, F. M. (1939): *Journ. Amer. Med. Assoc.*, cxiii. 1293-1299.
58. MONROE, R. T. (1939): "Chronic Arthritis," In Oxford Loose-Leaf Medicine, The Oxford University Press, New York, chap. xv., pp. 367-404.
59. OWENS, C. A., WRIGHT, W. D., AND LEWIS, M. D. (1938): *Journ. Urol.*, xl. 847-853.
60. PAPURT, L. E. (1939): *Ohio State Med. Journ.*, xxxv. 743-746.
61. PARSONS, R. P. (1939): *U.S. Nav. Med. Bull.*, xxxvii. 67-73.
62. POUNDERS, C. M., AND GRAY, J. K. (1939): *South. Med. Journ.*, xxxii. 471-475.
63. RAWLS, W. B. (1939): *Journ. Amer. Med. Assoc.*, cxii. 2509-2510.
64. RAWLS, W. B., WEISS, SAMUEL, AND COLLINS, VERA L. (1939): *Ann. Int. Med.*, xii. 1455-1462.
65. ROPES, MARIAN W., BENNETT, C. A., AND BAUER, WALTER (1939): *Journ. Clin. Investigation*, xviii. 351-372.
66. ROSENOW, E. C. (1939): *Illinois Med. Journ.*, lxxv. 28-38.
67. SABIN, A. B. (1939): *Science*, lxxxix. 228-229; 1939, xc. 18-19.
68. SASHIN, DAVID, SPANBOCK, JOSEPH, AND KLING, D. H. (1939): *Journ. Bone and Joint Surg.*, xxi. 723-734.
69. SCHULTZ, M. P., AND ROSE, EDYTHE J. (1939): *Pub. Health. Rep.*, liv. 248-263.

70. Scull, C. W., Bach, T. F., and Pemberton, Ralph (1939): *Ann. Int. Med.*, xii. 1463-1472.
71. Sherwood, K. K., and Hutchins, L. R. (1939): *Northwest Med.*, xxxviii. 257-260.
72. Sherwood, K. K., and Thomson, Marian E. (1939): *Journ. Amer. Dietet. Assoc.*, xv. 1-4.
73. Simmons, E. E., and Dunn, F. L. (1939): *Arch. Phys. Therapy.*, xx. 547-553.
74. Smith-Petersen, M. N. (1939): *Journ. Bone and Joint Surg.*, xxi. 269-288.
75. Snyder, R. G., Traeger, Cornelius, and Kelly, LeMoyne (1939): *Ann. Int. Med.*, xii. 1672-1681.
76. Spink, W. W. (1939): *Amer. Journ. Med. Sci.*, cxcviii. 35-39.
77. Spink, W. W., and Flink, E. B. (1939): *Bull. Minnesota Med. Foundation*, i. 26-29.
78. Steinberg, C. L., and Suter, Louise C. (1939): *Arch. Int. Med.*, lxiv. 483-492.
79. Steinbrocker, Otto (1939): *Ann. Int. Med.*, xii. 1917-1939.
80. Swaim, L. T. (1939): *Journ. Bone and Joint Surg.*, xxi. 983-991.
81. Swett, P. P. (1939): *New York State Journ. Med.*, xxxix. 2125-2131.
82. Swift, H. F., and Brown, T. M. (1939): *Science*, lxxxix. 271-272.
83. Tarsy, J. M. (1939): *Indust. Med.*, viii. 186-193.
84. Taussig, Helen B. (1939): *Journ. Pediat.*, xiv. 581-592.
85. Tegner, W. S. (1939): *Ann. Rheumat. Dis.*, i. 249-303.
86. Thomas, Caroline B., and France, Richard (1939): *Bull. Johns Hopkins Hosp.*, lxiv. 67-77.
87. Tobias, Norman (1939): *Int. Clin.*, (S. 2), iii. 173-182.
88. Toumey, J. W., Jr. (1939): *Surg., Gynec. and Obst.*, lxviii. 1029-1037.
89. Waugh, J. R., and Dawber, T. R. (1939): *Amer. Journ. Syph., Gonor. and Ven. Dis.*, xxiii. 477-489.
90. Wright, L. T., and Logan, Myra (1939): *Arch. Surg.*, xxxix. 108-121.

A STUDY OF CERTAIN BLOOD TESTS WHICH REVEAL COLLOIDAL ABNORMALITIES IN RHEUMATIC CONDITIONS*

By H. L. MILLES and H. B. SALT

Introduction

In chronic rheumatic conditions in which the blood is often characterised by a decreased suspension stability, there often occur alterations in the amounts, proportions, or nature of the proteins and perhaps other colloidal blood constituents. Discussions of these colloidal abnormalities have been made fre-

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quently and have been summarised by Race[1] and by other authorities. In general, it is concluded that the suspension stability depends in some way upon the colloidal state of the blood. More recent work has confirmed that in rheumatoid arthritis plasma globulins, especially euglobulin and fibrinogen, tend to rise while albumin tends to fall,[2] and that a determination of the suspension stability is a simple way of appraising these changes in the blood. In a study of serum proteins in rheumatoid disease by Scull *et al.*[3] it is especially remarked that both the actual levels of albumin and globulin, as well as their ratio, are to be remembered in considering abnormal colloidal systems in rheumatism. Ropes *et al.*[4] have confirmed that there is no absolute correlation between the blood suspension stability and the concentration of any of the plasma protein fractions, and they conclude that variations in stability are due to variations in the colloidal state of the plasma as a whole. This conclusion admits possibilities that substances other than proteins may contribute to the colloidal equilibrium, and that the effects of qualitative changes in the proteins may be of great importance. Indeed, albumin and globulin may not be distinct entities separable by chemical precipitation, an opinion discussed with other aspects of the problem by Davison.[5] It thus appears to be of less value to estimate the protein fractions in a rheumatic blood than to carry out the suspension stability test, in which the behaviour of the red cells furnishes an indication of the state of the colloidal system of which they form part.

Many other non-specific tests have been devised for the detection of abnormalities in the state of the blood in various diseases, notably tuberculosis and liver disorders. Though these are more concerned with the precipitability of the plasma colloids, they bear some similarity to the suspension stability test, especially in their interpretation. A study of certain of these tests has been made by applying them to blood samples, which were collected primarily for routine suspension stability tests on 140 unselected adult persons afflicted with rheumatism or allied disease.

Experimental

Four tests were carried out on each blood sample, the specimen consisting of about 11 ml. venous blood, of which 6 ml. were promptly oxalated with 12 mg. potassium oxalate in one tube

and the remainder allowed to clot for serum in a second tube. The oxalated whole blood was used for determination of suspension stability (S.S.) and packed cell volume (P.C.V.), while the residual plasma was taken for the formol-gel test (F.G.T.). The serum was used for the calcium chloride heat coagulation test and the mercuric chloride flocculation test.

Suspension Stability Test (*Erythrocyte Sedimentation Test*).—This was determined without delay (usually at once, never later than three hours after collection) in 5 ml. capacity graduated centrifuge tubes, using undiluted oxalated blood by the method of Collins *et al.*[6] After two hours' settling, the blood was centrifuged for determination of packed cell volume, and the crude S.S. value at one hour was corrected on the basis of the P.C.V. reading by the formula:

Corrected S.S. = Crude S.S. + f (42 – P.C.V.), where factor f = 1·5 if P.C.V. is below 42 per cent., or 1·0 if P.C.V. is above 42 per cent., taking proper account of algebraic signs.

The S.S. test was regarded as a standard method of assessing the colloidal condition of the blood samples and results of the other tests were therefore related to these. Previous experience with the S.S. test had proved that healthy blood usually shows a stability of 90 per cent. or over, though sometimes it may be as low as 85 per cent. With very few exceptions, the most unstable bloods yield a minimum corrected stability value of 55 per cent., the lowest value ever obtained being 53 per cent. It must be noted that these values are one-hour corrected S.S. figures; crude S.S. values are found to spread over a wider range owing to the effects of varying cell volumes.

It was decided to divide the results into three arbitrary groups of almost equal range, namely, corrected S.S. 100 to 85, 84 to 70, and 69 to 53. The blood samples were unselected, and the results were placed into these three groups as they were obtained. However, an inspection of the accumulating results showed most features of interest in the low S.S. group, so that after thirty blood specimens had been tested in the high S.S. group and thirty in the medium S.S. group, only bloods of low suspension stability were continued with, until eighty results were available in the low S.S. group. Later this last group was subdivided into almost equal halves, separating thirty-eight blood specimens where the corrected S.S. lay between sixty-nine and sixty, from forty-two blood specimens where the range was

fifty-nine to fifty-three. This subdivision served to mark off clearly the group of exceptionally unstable bloods.

The Formol Gel Test (*Aldehyde Reaction*).—This test, which depends upon the formation of a gel when formaldehyde is added to plasma, has been studied in chronic rheumatism by Gibson and Richardson,[7] and in acute rheumatism by Green *et al.*[8] The technique of these authors was adopted, and the test applied to the clear plasma of each blood sample after the suspension stability had been determined and the blood centrifuged at 3,000 r.p.m. for fifteen minutes. The arrangement of the test and method of recording the results is indicated in the following table:

Tube No.:	1 *Ml.*	2 *Ml.*	3 *Ml.*	4 *Ml.*	5 *Ml.*	6 *Ml.*
Plasma	0·5	0·45	0·4	0·35	0·3	0·25
Saline	0·0	0·05	0·1	0·15	0·2	0·25
18 per cent. formalin ..	0·04	0·04	0·04	0·04	0·04	0·04

Mix, leave eighteen hours at room temperature, examine for gel formation.

Results: No gel=0. Partial gelation in tube 1=1-plus or 2-plus. Complete gelation in tube 1=3-plus, in tube 2=4-plus, in tube 3=5-plus, etc., up to 8-plus.

The formol-gel test, like the suspension stability test, is not specific for any pathological condition; in fact, positive reactions of the plasma are likely in any disease with an elevated plasma globulin, and the F.G.T. merely gives an indication of the colloidal state of the blood.

A good degree of correlation between the formol-gel reaction and the suspension stability of the blood has been obtained by both the authors quoted above. In the present instance, the F.G.T. was adopted as an accessory to the S.S. test, for comparison with the other tests described below and as a means of detecting anomalous S.S. results if they occurred.

The Calcium Chloride Heat Coagulation Test (*Weltmann Reaction*).—The Weltmann serum coagulation reaction[9] has been studied in many diseases, amongst which are rheumatic conditions.[10, 11] In America, Levinson and co-workers have made a close study of the reaction in tuberculosis, rheumatic fever and other diseases, and valuable discussions are given in their publications,[12, 13 14, 15] together with a description of the technique,

especially well recorded with photographs of the reaction results in their paper of 1939. Essentially the test is as follows: From a stock solution of hydrated calcium chloride, 10 per cent. $CaCl_2,6H_2O$, ten dilutions consisting of 0·1 per cent., 0·09 per cent., 0·08 per cent., 0·07 per cent., 0·06 per cent., 0·05 per cent., 0·04 per cent., 0·03 per cent., 0·02 per cent., and 0·01 per cent., are prepared freshly each day and numbered one to ten, beginning with the strongest. (This arbitrary numbering is quite unnecessary, but has been adopted so far by previous workers. The present authors have retained the numbering system, but would urge that the calcium chloride concentrations themselves are adequate designations, especially if expressed as decigrams per litre to keep in whole numbers. The order of such numbering, however, would be the reverse of the arbitrary numbering actually adopted.) Five ml. of each dilution are placed respectively in test tubes numbered one to ten, followed by 0·1 ml. unhæmolysed serum. After well mixing, the tubes are placed in a boiling-water bath for fifteen minutes, then removed and examined for coagulation, which is usually very easily distinguished from turbidity. The number of tubes in which coagulation occurs is called the serum coagulation band (S.C.B.). Healthy serum gives an S.C.B. of six; or there might be very slight coagulation also in tube number seven, which is recorded as S.C.B. $6\frac{1}{2}$. Abnormal sera may give values above or below this figure. In order to preserve a uniform terminology, the descriptive title "calcium chloride heat coagulation test" is adopted here. The test was chosen for study because others have already obtained interesting results in rheumatic conditions, although the coagulation band has not always been found to parallel the suspension stability. The mechanism of the reaction is obscure, though obviously different results must depend on differences in the coagulable colloids of the serum.

The Mercuric Chloride Flocculation Test (Takata-Ara Reaction).—This reaction, first described by Takata and Ara in 1925, and afterwards much studied in Germany as a test for liver disease, became the subject of investigations by several workers in America. Crane[16] reviewed its history, modified the technique and studied liver disease. Kirk[17] reviewed all the previous results in the literature and contributed his own experiences. Bowman and Bray[18] emphasised the non-specific nature of the reaction and its dependence on the amounts or proportions of

the serum proteins. The history of the test was again reviewed by Chasnoff and Solomon[19] and their method of carrying out the reaction and interpreting the results was carefully described. In the present study this method was adopted, which is essentially as follows:

One ml. 0·9 per cent. sodium chloride is placed in each of six small tubes. To the first tube, 1·0 ml. serum is added and mixed; 1·0 ml. of the mixture is then removed and added to the saline in the second tube; this procedure is continued throughout the six tubes, 1·0 ml. from the last tube being discarded, leaving serum dilutions of 1 : 2 to 1 : 64. To each is added 0·25 ml. 10 per cent. sodium carbonate, followed, after mixing, by 0·15 ml. 0·5 per cent. mercuric chloride. All the tubes are then thoroughly shaken and set aside at room temperature for twenty-four hours, when a pearly flocculum may have developed, indicating a positive reaction. Any other deposit is disregarded. If the flocculation is definite in four or more tubes, a strong positive (3-plus) result is indicated; if definite but slight in three or four tubes, a positive (2-plus) result; if definite but minimal in three tubes, a weak positive (1-plus) result; all other results are negative. The method of interpreting the results is important, as different investigators have applied different criteria for evaluation of the findings. The 1-plus positive results here recorded were almost always indicated by the last three tubes showing the flocculum.

It is emphasised by Chasnoff and Solomon that the mercuric chloride reaction is not specific for liver disease, and that it is likely to be positive whenever the albumin-globulin ratio in the serum is decreased. This is the most important, though not the sole factor, in the mechanism of the reaction; a conclusion supported by the results of Taran and Lipstein,[20] who studied the test in tuberculous patients. Hitherto the test does not seem to have been applied to the blood of rheumatic patients, but its trial is justified by the essentially non-specific nature of the test and the dependence of the results upon the colloidal state of the serum. Positive results have been obtained in active tuberculosis where low suspension stabilities are found, and in kala-azar, where the formol gel reactions are characteristically intense, though the greatest incidence of positive mercuric chloride tests is to be found in hepatic cirrhosis.

Discussion of Results

The experimental findings are recorded in Tables I, II, IIIA and IIIB, arranged in order of decreasing suspension stability

Table I.—Thirty Cases with Corrected S.S. in the Range 101 to 85.

Case No. and Sex.	*Diagnosis, etc.*	*Crude S.S., 1 Hour.*	*Corrected S.S., 1 Hour.*	*P.C.V. per Cent.*	*Formol Gel Test.*	*Serum Coagulation Band.*	*Mercuric Chloride Flocculation.*
185, F.	R.A., Group 2	90	101	35	0	7½	0
198, F.	(?) R.A.	77	100	27	0	7	0
104, M.	Fibrositis	97	97	42	0	6	0
132, F.	(?) R.A.	96	96	42	0	6½	0
123, F.	Fibrositis	92	95	40	0	6	0
125, F.	Osteo-arthritis	89	95	38	0	6	0
66, M.	(?) Strain	92	94	41	0	6	0
186, M.	Fibrositis, peri-articular	96	94	44	0	8½	0
181, F.	R.A., Group 1	94	93	43	0	7½	0
87, M.	R.A., Group 1	99	93	48	0	6	0
92, M.	Fibrositis, peri-articular	95	92	45	0	6	0
126, M.	Lumbago, joint pain	96	92	46	0	7	0
127, M.	(?) R.A.	95	92	45	0	6	0
83, M.	Fibrositis	95	91	46	0	6½	0
70, F.	(?) pre-R.A.	92	91	43	0	6½	0
137, M.	(?) R.A.	90	90	42	0	6	0
175, M.	R.A. (definite)	84	90	38	0	8	0
94, F.	Fibrositis	80	89	36	0	6½	0
152, M.	R.A., Group 2	91	89	44	0	7	0
121, F.	Fibrositis	89	88	43	0	5	0
133, F.	Fibrositis	88	88	42	0	6	0
134, M.	R.A., Group 2	90	88	44	0	7½	0
162, M.	Fibrositis	85	88	40	0	7	0
164, M.	Chronic gout	93	88	47	0	7	0
75, M.	Fibrositis	82	88	38	0	5	0
89, M.	Erythema nodosum	90	88	44	0	6½	0
47, M.	Gout	93	87	48	0	6½	0
59, F.	R.A., Group 1	80	86	38	0	5½	0
91, M.	Synovitis	92	86	48	0	5½	0
81, F.	Osteo-arthritis	78	86	37	0	6	0

and divided into groups corresponding to corrected S.S. values of 101 to 85, 84 to 70, 69 to 60, and 59 to 53. The first two cases of Table I are examples of anæmia in the absence of diminished suspension stability, a phenomenon discussed by Collins *et al.*,[6] which explains the apparently absurd values of 100 or over for the corrected S.S. In every other respect the corrected S.S. values are regarded as the most satisfactory characteristics of the blood samples upon which to base a grouping and comparison of results.

Comparing the formol-gel test with suspension stabilities, it

is immediately apparent that with only one exception (partial gelation) the F.G.T. is negative whenever the corrected S.S. is above seventy (fifty-nine cases out of sixty). Where the corrected S.S. is below seventy, the F.G.T. is usually positive, the incidence being seventy-three times out of eighty. The seven

TABLE II.—THIRTY CASES WITH CORRECTED S.S. IN THE RANGE 84 TO 70.

Case No. and Sex.	*Diagnosis, etc.*	*Crude S.S., 1 Hour.*	*Corrected S.S., 1 Hour.*	*P.C.V. per Cent.*	*Formol Gel Test.*	*Serum Coagulation Band.*	*Mercuric Chloride Flocculation.*
84, F.	R.A. Group 1	81	84	40	0	6½	0
179, M.	Gout, synovitis	84	84	42	0	7	0
160, F.	Fibrositis	80	83	40	0	6½	0
153, F.	R.A., Group 2	80	83	40	0	6½	0
72, F.	Fibrositis	75	83	37	0	7	0
158, M.	R.A., Group 2	85	82	45	0	6½	0
195, F.	R.A., Group 2	71	82	35	0	8	0
111, F.	Fibrositis	73	82	36	0	6	0
112, F.	Osteo and rheumatoid arthritis	72	81	36	0	5	0
172, F.	R.A., Group 1	81	81	42	0	7	0
146, M.	R.A., Group 3	80	80	42	0	4½	0
62, F.	(?) R.A.	77	79	41	0	4½	0
86, M.	Fibrositis, strain	81	79	44	2-plus	6	0
122, F.	R.A., Group 2	71	79	37	0	6	0
167, M.	R.A., Group 2	81	79	44	0	7	0
155, F.	R.A., Group 2	78	78	42	0	7½	0
197, F.	R.A., Group 2	72	78	38	0	7	0
144, F.	Fibrositis	79	76	45	0	5½	0
151, M.	Rheumatic fever (mild)	80	76	46	0	6½	0
58, M.	R.A., Group 1	80	75	47	0	6½	0
76, F.	Fibrositis	75	75	42	0	5½	0
165, M.	Chronic gout	72	75	40	0	7	0
191, F.	R.A., Group 1	73	75	41	0	7	0
192, F.	R.A., Group 2	59	74	32	0	6½	0
145, M.	R.A., Group 2	76	73	45	0	5	0
61, M.	R.A., Group 2	67	72	39	0	4½	0
103, F.	R.A. (severe)	72	72	42	0	4½	0
163, M.	Spondylitis ankylosis	75	72	45	0	5	0
147, F.	R.A., Group 2	70	70	42	0	6	0
178, M.	R.A., Group 1	67	70	40	0	7½	0

instances of negative formol-gel reactions in bloods of corrected S.S. less than seventy are discussed later. A comparison of corrected S.S. and F.G.T. results is summarised in Table IV on page 38.

In general, the correlation between the two tests found by Gibson and Richardson[7] and by Green *et al.*[8] is confirmed, the present results being even more clear cut, probably because corrected S.S. values are adopted instead of crude S.S. values. It is apparent that the F.G.T. is less sensitive than the S.S. test,

but that it can be especially useful in further characterising those bloods whose suspension stabilities lie in the lowest range.

The correlation existing between the F.G.T. and anæmia is

TABLE IIIA.—THIRTY-EIGHT CASES WITH CORRECTED S.S. IN THE RANGE 69 TO 60.

Case No. and Sex.	*Diagnosis, etc.*	*Crude S.S., 1 Hour.*	*Corrected S.S., 1 Hour.*	*P.C.V. per Cent.*	*Formol Gel Test.*	*Serum Coagulation Band.*	*Mercuric Chloride Flocculation.*
120, F.	Fibrositis	70	69	43	0	6	0
50, M.	R.A., (three months)	69	69	42	0	5½	1-plus
60, M.	R.A., Group 1	73	69	46	1-plus	6½	0
105, F.	Rheumatoid arthritis	57	69	34	3 ,,	5	1-plus
210, M.	R.A., Group 2	69	69	42	3 ,,	6½	0
138, F.	R.A., Group 3	59	68	36	3 ,,	4½	0
99, F.	Rheumatoid arthritis	61	67	38	3 ,,	6	1-plus
129, F.	R.A., Group 1	64	67	40	3 ,,	7	0
154, F.	(?) R.A., (six months)	67	67	42	0	6	0
77, M.	Osteo-arthritis	61	66	39	1 ,,	6	1-plus
166, M.	R.A., Group 2 (five months)	60	66	38	0	7½	0
106, M.	Fibrositis	71	65	48	5 ,,	5½	2-plus
109, M.	R.A., Group 3	71	65	48	3 ,,	6	0
110, M.	R.A., Group 3	66	65	43	3 ,,	5½	0
131, F.	R.A. (no symptoms for two years)	57	67	37	0	6	0
135, M.	R.A., Group 2	68	65	45	2 ,,	4½	0
161, F.	R.A., Group 3	45	65	29	6 ,,	6½	0
80, F.	R.A., Group 2	61	64	40	3 ,,	4	0
101, F.	Fibrositis	65	64	43	3 ,,	6½	1-plus
177, M.	R.A., Group 3	65	64	43	3 ,,	8	0
115, M.	Spondylitis ankylosis (early)	61	63	41	3 ,,	4½	0
184, M.	R.A., Group 1	66	63	45	0	6½	0
96, F.	Rheumatoid arthritis	64	62	44	3 ,,	6	0
102, M.	Meningococcal septicæmia	62	62	42	5 ,,	1½	0
114, M.	R.A., Group 3	59	62	40	2 ,,	6	2-plus
119, F.	Gonococcal arthritis	51	62	35	4 ,,	7	0
173, M.	R.A., Group 2	64	62	44	3 ,,	6½	0
180, M.	R.A., Group 3	64	62	44	4 ,,	6½	0
56, F.	Muscular stiffness	52	61	36	4 ,,	6½	1-plus
65, F.	R.A., Group 2	55	61	38	3 ,,	5½	0
140, M.	R.A., Group 3	61	61	42	4 ,,	5½	0
143, F.	R.A., Group 3 (fifteen years)	50	61	35	0	4	0
168, M.	R.A., Group 3	38	61	27	4 ,,	5½	0
183, M.	R.A., Group 3	63	61	44	3 ,,	5½	0
98, F.	Rheumatoid arthritis	45	60	32	4 ,,	4	1-plus
100, M.	Rheumatoid arthritis	57	60	40	4 ,,	5	0
170, F.	R.A., Group 3	49	60	35	7 ,,	7	1-plus
171, M.	R.A., Group 2	60	60	42	2 ,,	7	0

also confirmed by present results. Table V on page 38 shows the relationship between the degree of positivity of the formol-gel reactions and the average packed cell volumes.

As the formol-gel reactions become more intense, the average

P.C.V. falls, as does the average crude S.S., but the phenomenon is apparently unrelated to the true or corrected S.S., which is fairly constant throughout the range of formol-gel results. On

TABLE IIIB.—FORTY-TWO CASES WITH CORRECTED S.S. IN THE RANGE 59 TO 53.

Case No. and Sex	*Diagnosis, etc.*	*Crude S.S., 1 Hour.*	*Corrected S.S., 1 Hour.*	*P.C.V. per Cent.*	*Formol Gel Test.*	*Serum Coagulation Band.*	*Mercuric Chloride Flocculation.*
44, F.	Fibrositis	51	59	37	3-plus	5	0
53, M.	R.A. (severe)	47	59	34	5 ,,	3	0
93, F.	R.A., Group 3	42	59	31	7 ,,	5½	2-plus
128, M.	Gout	59	59	42	3 ,,	5	0
136, F.	R.A., Group 2	57	59	41	1 ,,	5	0
74, F.	Fibrositis (R.A.)	49	58	36	4 ,,	3	0
113, F.	R.A., Group 3	44	58	33	8 ,,	4	3-plu
118, M.	R.A., Group 2	53	58	39	4 ,,	6	1 ,,
124, F.	Rheumatoid arthritis	58	58	42	3 ,,	6	0
141, F.	R.A., Group 3	46	58	34	6 ,,	5	0
157, M.	R.A., Group 2	52	58	38	3 ,,	6½	0
174, F.	Rheumatoid arthritis	58	58	42	3 ,,	7½	0
182, M.	R.A., Group 3	58	58	42	5 ,,	4½	0
199, F.	R.A., Group 3	43	58	32	4 ,,	5½	0
204, F.	Rheumatoid arthritis	52	58	38	3 ,,	6½	0
46, M.	Rheumatoid arthritis	55	57	41	3 ,,	7	0
142, F.	R.A., Group 3	46	57	35	5 ,,	4½	0
156, F.	Gout	39	57	30	3 ,,	5	0
169, M.	R.A., Group 3	55	57	41	3 ,,	7	0
190, M.	Spondylitis, ankylosing	48	57	36	5 ,,	6	1-plus
194, M.	R.A., Group 3	43	57	33	4 ,,	5½	0
207, F.	R.A., Group 3	51	57	38	4 ,,	5½	0
73, M.	Osteo-arthritis (early)	61	56	47	3 ,,	5	0
90, M.	Gout	56	56	42	3 ,,	5½	0
117, F.	Rheumatoid arthritis	54	56	41	3 ,,	6½	0
130, F.	R.A., Group 3	50	56	38	3 ,,	5½	0
149, F.	R.A., Group 2	48	56	37	4 ,,	5	0
150, M.	R.A., Group 3	54	56	41	3 ,,	5	0
159, M.	R.A., Group 2	57	56	43	4 ,,	7	0
187, M.	Rheumatoid arthritis	50	56	38	6 ,,	5½	0
188, M.	R.A., Group 3	56	56	42	3 ,,	6½	0
196, M.	R.A., Group 1	41	56	32	5 ,,	7	1-plus
202, F.	R.A., Group 2	47	56	36	4 ,,	6	0
57, F.	R.A., Group 3	55	55	42	3 ,,	5½	1-plus
148, M.	R.A., Group 3	53	55	41	4 ,,	5	0
189, M.	Rheumatoid arthritis	47	55	37	4 ,,	6	0
200, M.	R.A., Group 3	47	55	37	4 ,,	5	0
201, M.	R.A., Group 3	44	55	35	5 ,,	3	0
203, F.	R.A., Group 3	43	54	35	5 ,,	6	0
193, F.	R.A., Group 3	50	53	40	4 ,,	6½	0
88, M.	Acute rheumatic fever	50	53	40	5 ,,	2½	0
116, M.	Acute rheumatic fever	48	53	39	4 ,,	0	0

the other hand, many anæmic bloods occur in Tables I and II, where the F.G.T. is quite negative and the S.S. ranges from normal to seventy, showing that a low S.S. is a necessary characteristic of a blood which gives a positive F.G.T.

In contrast to the formol-gel test and in similarity to the suspension stability test, the calcium chloride heat coagulation

TABLE IV

Corrected S.S. Range.	*Distribution of F.G.T. Results.*								
	0	1-2	3	4	5	6	7	8-*plus.*	
101–85	30	0	0	0	0	0	0	0	Cases out of 30
84–70	29	1	0	0	0	0	0	0	Cases out of 30
69–60	7	5	15	7	2	1	1	0	Cases out of 38
59–53	0	1	16	13	8	2	1	1	Cases out of 42

TABLE V

No. of Cases.	*F.G.T.*	*Average Crude S.S.*	*Average Corrected S.S.*	*Average P.C.V.*
31	3-plus	58	61	41
20	4-plus	50	58	37
10	5-plus	51	58	38
3	6-plus	47	60	34
2	7-plus	45	59	33
1	8-plus	44	58	33

reaction appears to be very sensitive, showing a fairly wide range of values for the serum coagulation band in each of the S.S. groups. These values are summarised in Table VI:

TABLE VI

Corrected S.S. Range.	*Average S.C.B. Value.*	*Distribution of S.C.B. Values.*												
		0	1½	3	3½	4	4½	5	5½	6	6½	7	7½ 8 8½	=*S.C.B.*
		½ 1	2 2½											
101–85 ..	6½							2	2	10	6	5	5 cases	
84–70 ..	6						4	3	2	4	7	7	3	,,
69–60 ..	6		1			3	3	2	7	8	8	4	2	,,
59–53 ..	5½	1	1	3	0	1	2	10	8	6	5	4	1	,,

Serum coagulation band values outside the range of six to seven are regarded as showing a " shift to the left or to the right." It must be recognised clearly that a shift to the left indicates an

exudative condition, while a shift to the right indicates a fibrotic process, but that the occurrence of both pathological changes together may result in an S.C.B. value of six to seven, indistinguishable from a result given by a healthy serum. Thus all values of six to seven are not necessarily normal. One can therefore rely only upon abnormal S.C.B. values for information about pathological conditions. The table indicates that when the S.S. is high few of the S.C.B. values show deviation to the left or right. As the S.S. becomes progressively lower, there are even fewer deviations to the right but steadily more deviations to the left. However, a close inspection of individual results in Tables I, II, IIIA, and IIIB makes it apparent that an exact parallel between S.C.B. and S.S. cannot be found.

Studying the S.C.B. results obtained at different levels of cell volume, it appears that P.C.V. variations have no influence on the serum coagulation results. Table VII indicates the relationships:

TABLE VII

Range of P.C.V.	*From Table I.*		*From Table II.*		*From Table IIIA.*		*From Table IIIB.*	
	Mean S.C.B.	*No. of Cases.*	*Mean S.C.B.*	*No. of Cases.*	*Mean S.C.B.*	*No. of Cases.*	*Mean S.C.B.*	*No. of Cases.*
26–30 ..	7	1	—	0	6	2	5	1
31–35 ..	7½	1	7	2	5	5	5	10
36–40 ..	6	8	6	11	6	11	5	16
41–45 ..	6½	14	6	15	6	17	6	14
46–50 ..	6½	6	6½	2	6	3	5	1

In this respect, therefore, the calcium chloride heat coagulation test differs from the formol-gel test. The mean S.C.B. values shown in the table again suggest a general correlation with the S.S. results, for the S.C.B. values corresponding to the high stability bloods are seen to fall within the normal range of six to seven, while those corresponding to the low-stability bloods exhibit lower values.

The high globulin content and low albumin-globulin ratio often found in blood of low suspension stability had suggested the possibility that a number of positive mercuric chloride flocculation tests would be discovered in this series. This expectation was realised, there being complete absence of positive tests from bloods of S.S. greater than seventy, but sixteen positive

results where the S.S. was below seventy. The occurrence of these positive reactions is shown in Table VIII:

TABLE VIII

Corrected S.S. Range.	*Distribution of Mercuric Chloride Flocculation Reactions.*				
	Negative.	1-*plus.*	2-*plus.*	3-*plus.*	*Reaction Result.*
101–85 ..	30	0	0	0	Cases out of 30
84–70 ..	30	0	0	0	Cases out of 30
69–60 ..	28	8	2	0	Cases out of 38
59–53	36	4	1	1	Cases out of 42

The incidence of positive reactions is rather low, and of the positive tests the majority were only weakly positive. Nevertheless the fact was established that bloods which yielded these positive results could thus be differentiated from other bloods of low suspension stability which failed to give positive flocculations.

When the positive flocculation tests are compared with the formol-gel results (Table IX) it appears that, with only one exception, the formol-gel tests were also positive, often to a high degree:

TABLE IX

No. of Cases.	*Mercuric Chloride Flocculation Result.*	*Distribution of F.G.T. Results.*							
		0	1-2	3	4	5	6	7	8-*plus.*
12 ..	1-plus	1	1	4	3	2	0	1	0 cases
3 ..	2-plus	0	1	0	0	1	0	1	0 ,,
1 ..	3-plus	0	0	0	0	0	0	0	1 ,,

A similar comparison with the calcium chloride heat coagulation test (Table X) reveals that only about half the bloods which gave positive flocculation yielded also abnormal serum coagulation bands, but that these were always deviated to the left:

TABLE X

No. of Cases.	*Mercuric Chloride Flocculation Result.*	*Distribution of S.C.B. Values.*						
		0 ½ 1	1½ 2 2½	3 3½ 4	4½ 5 5½	6 6½ 7	7½ 8 8½	=*S.C.B.* (*Values Grouped*).
12	1-plus	0	0	1	3	8	0 cases	
3	2-plus	0	0	0	2	1	0 ,,	
1	3-plus	0	0	1	0	0	0 ,,	

Moreover, it was found that the P.C.V. was frequently reduced below normal in those bloods which showed positive mercuric chloride flocculations (Table XI). This finding recalls a similar correlation between highly positive formol-gel tests and low cell volumes, and suggests that there is something in common between the phenomena of gelation of plasma with formalin and flocculation with mercuric chloride:

TABLE XI

No. of Cases.	*Mercuric Chloride Flocculation.*	*Distribution of P.C.V. Values.*			
		31–35	36–40	41-45	46–50
12	1-plus	4	5	3	0 cases
3	2-plus	1	1	0	1 ,,
1	3-plus	1	1	0	0 ,,

Finally, the relationships between the formol-gel reactions and serum coagulation bands were studied to reveal any correlation. It was found (Table XII) that the majority of bloods with negative formol-gel reactions had serum coagulation bands falling with the normal range. As the F.G.T. became progressively more strongly positive, a progressively greater proportion of shortened coagulation bands was found, while the few lengthened coagulation bands shown by the formol-gel negative bloods disappeared entirely:

TABLE XII

No. of Cases.	*Formol-Gel Reaction.*	*Distribution of S.C.B. Values.*											
		0 ½ 1	1 ½ 2 2 ½	3	3½	4	4½	5	5½	6	6½	7	7½ 8 8½
66	Negative	0	0	0	0	1	4	5	5	16	14	12	9 cases
7	1-2-plus	0	0	0	0	0	1	1	0	3	1	1	0 ,,
31	3-plus	0	0	0	0	1	2	6	6	4	7	3	2 ,,
20	4-plus	1	0	1	0	1	0	4	5	3	3	2	0 ,,
10	5-plus	0	2	2	0	0	2	0	1	2	0	1	0 ,,
3	6-plus	0	0	0	0	0	0	1	1	0	1	0	0 ,,
2	7-plus	0	0	0	0	0	0	0	1	0	0	1	0 ,,
1	8-plus	0	0	0	0	1	0	0	0	0	0	0	0 ,,

So far, the results have been discussed with little or no reference to the clinical conditions of the subjects from whom the blood specimens were obtained. None of the tests selected for study is specific for the rheumatic state, so that there is little

chance of any definite correlation between the results of these tests and the clinical subdivisions of rheumatic disease. Moreover, the experimental studies were not especially directed towards an investigation of this aspect of the problem. Nevertheless, certain comments seem to be justified.

The seven completely negative formol-gel reactions found in the S.S. Group 69 to 70 (Table IIIA) were derived from five cases of rheumatoid arthritis of only short duration (all under nine months) in which the clinical symptoms were so indefinite as to render diagnosis doubtful; one case of mild rheumatoid arthritis previously treated with gold injections, leaving the patient symptom-free for two years; and one case of fifteen years' history of rheumatoid arthritis, clinically severe and still active, although three courses of gold treatment had been given. In this last case the negative formol-gel test was confirmed by repetition, and the result is exceptional. In the other cases the negative gel tests correspond closely with the observed clinical conditions, and appear to modify the conclusions concerning activity of the disease, which the suspension stabilities alone indicate.

Gibson and Richardson[7] found that some cases of gout gave weaker formol-gel reactions than the suspension stabilities warranted. In the present series, seven cases diagnosed clinically as gout are recorded, but only one showing unusual results (Case 156, Table IIIB) need be mentioned, in which the hæmoglobin was 8·6 grammes per cent.; plasma uric acid, 7·44 mg. per 100 ml.; whole blood uric acid, 6·00 mg. per 100 ml.; and F.G.T. only 3-plus; though the P.C.V. was only 30 per cent. and the corrected S.S. 57 per cent.

Observations of the results of the calcium chloride heat coagulation test in rheumatism have not yet been made sufficiently for their significance to be recognised clearly. In the present series, noting the extreme values first, exceptionally short serum coagulation bands were found in the acute stage of rheumatic fever (Cases 116 and 88, Table IIIB), corresponding to very low suspension stabilities and highly positive formol-gel tests. A third case of rheumatic fever (No. 151, Table II), with a much greater stability and negative formol-gel test, gave an S.C.B. in the normal range corresponding with a clinically mild condition of four weeks' duration, without heart involvement. Another case (No. 102, Table IIIA), at first thought to be rheumatic but afterwards believed to be a meningococcal septicæmia

which responded to M. and B. 693, also yielded a very low S.C.B., though the S.S. was reduced to only sixty-two. Of the three S.C.B. values of three, two were given by severe cases of rheumatoid arthritis and one by a case of toxic fibrositis, having also some rheumatoid arthritis of the knees.

The remaining S.C.B. values are best studied in Table XIII, in which the results are summarised with reference to the clinical grouping of the cases. A classification of rheumatoid arthritis in this table has been made as follows: Group 1 includes chronic rheumatoids with good general health and without any recent exacerbation of joint symptoms. Group 2 represents sub-acute rheumatoids showing recent activity in the joints and some swelling but no œdema, with fair general health. Group 3 refers to acute rheumatoid arthritis or an acute phase in a chronic rheumatoid arthritis, with painful swollen joints and œdema and poor general health. Some of the rheumatoid cases were definite, but not grouped according to this plan, while others were so vague as to render the diagnosis doubtful.

Table XIII shows that the Group 2 rheumatoids and the other definite cases (ungrouped) often show a shift to the left in the S.C.B., and that this finding is even more definite in the Group 3 rheumatoids. However, other clinical types also show a shift to the left sometimes, while some of the rheumatoids, especially the less severe cases, show a shift to the right. Reference to Table VI shows that none of these deviations is very extreme in extent, excepting the six cases already noted with serum coagulation bands between 0 and 3. It appears, therefore, that rheumatoid arthritis, particularly the severe forms of the disease, reveals itself as an exudative process by showing a moderate shift to the left in the coagulation band as determined by the calcium chloride heat coagulation test. Where cases of rheumatoid arthritis show a shift to the right in the coagulation band, it would seem that the condition is less severe and possibly has a better prognosis.

Referring, finally, to Table XIII, it is seen that the mercuric chloride flocculation test yields positive results in various clinical conditions, and it is presumed, therefore, that the reaction is indicative of plasma changes of a fundamental but non-specific nature. Of the sixteen positive reactions, only four were strongly positive. These were given by three cases of severe rheumatoid arthritis and one case of fibrositis. The remaining twelve

positive reactions were given by nine rheumatoids, one fibrositis, one osteo-arthritis, and one case of muscular stiffness which had followed rheumatic fever for three years. At present, the exact difference between flocculation-positive and flocculation-negative bloods from cases otherwise very similar remains obscure.

TABLE XIII

	No. of Cases.	S.S.Range			F.G.T.		S.C.B.			Mercuric Chloride Flocculation.	
		101 to 85	84 to 70	69 to 53	Positive.	Negative.	Left Shift.	Normal.	Right Shift.	Positive.	Negative.
Rheumatoid arthritis:											
Doubtful	7	5	1	1	0	7	1	6	0	0	7
Group 1	12	3	5	4	3	9	1	9	2	1	11
Group 2	27	3	11	13	12	15	7	15	5	1	26
Group 3	31	0	1	30	29	2	21	9	1	5	26
Ungrouped ..	17	1	1	15	13	4	7	8	2	4	13
Fibrositis	21	10	6	5	5	16	7	13	1	2	19
Osteo-arthritis ..	4	1	1	2	2	2	1	3	0	1	3
Gout	7	2	2	3	3	4	3	4	0	0	7
Rheumatic fever ..	3	0	1	2	2	1	2	1	0	0	3
Other cases ..	11	4	2	5	5	6	5	6	0	2	9

SUMMARY AND CONCLUSIONS

The use of non-specific tests for abnormal colloidal states in the blood is discussed. Four tests are described which were selected for an investigation of the blood in 140 cases of rheumatism or allied disease—namely, the suspension stability test, the formol-gel test, the calcium chloride heat coagulation test (Weltmann reaction), and the mercuric chloride flocculation test (Takata-Ara reaction). The mechanism of the tests and the significance of the results obtained therefrom are indicated.

The results of the blood tests are tabulated and discussed. The formol-gel test was almost always negative whenever the corrected suspension stability was above seventy. Negative formol-gel tests were also given by a few cases of early mild rheumatoid arthritis, although the suspension stabilities were in the range sixty-nine to sixty. Positive formol-gel tests of varying intensity were most usually obtained with bloods where the suspension stability was below seventy. Anæmic states,

revealed by diminished packed cell volume, accounted for the occurrence of more intense gel tests than the corrected suspension stabilities would seem to predict in such cases.

The calcium chloride heat coagulation test was found to yield substantially normal serum coagulation bands whenever the corrected suspension stability was high. As the stabilities progressively diminished through the series, the serum coagulation bands also diminished—*i.e.*, became deviated to the left—though an exact parallel between the suspension stability and the serum coagulation band could not be detected in every individual case. Variations in volume of packed cells had no apparent influence on the value of the serum coagulation bands. Negative formol-gel tests were usually associated with normal coagulation bands, while progressively more intense gel reactions were found to be accompanied by a progressive shift to the left in the serum coagulation band.

The mercuric chloride flocculation test was invariably negative whenever the corrected suspension stability was greater than seventy. Among eighty blood specimens of stability below seventy, sixteen positive flocculation tests were discovered. According to expectations, these sixteen bloods also showed positive formol-gel tests in almost every case, but showed abnormal serum coagulation bands in only about half the cases. The abnormal coagulation bands were always shortened—*i.e.*, deviated to the left. A reduction in the volume of packed cells was frequently associated with positive mercuric chloride flocculation reactions.

Comparing the results of the blood tests with the clinical conditions of the patients, it appears that both the suspension stability test and the calcium chloride heat coagulation test are very sensitive indicators of the extent of activity of rheumatic disease. But the two tests do not always run parallel. The significance of the serum coagulation band in rheumatism is not clearly understood, and extensive observations on this point should be made, as they would probably render the calcium chloride heat coagulation test as useful to the rheumatologist as is the suspension stability test. Already it has been found that severe rheumatoid arthritis is characterised by a moderate shift to the left in the serum coagulation band, and that rheumatic fever in the acute stage produces a much greater deviation to the left. An occasional shift to the right was found

in rheumatoid arthritis, and this would seem to be a sign of good prognosis. However, further observations are clearly desirable.

The usefulness of the formol-gel test is restricted to a confirmation of the significance of low suspension stabilities. Strongly positive gel-tests reinforce the meaning of the low stabilities, and are often accompanied by low packed cell volumes, while occasional weakly positive or negative gel tests may modify the significance attributed to low stabilities.

Positive mercuric chloride flocculation tests are occasionally to be found where suspension stabilities are low, especially where the formol-gel test is strongly positive and volume of packed cells diminished. While such results are most frequently found in rheumatoid arthritis, the exact meaning of the positive flocculation tests remains obscure, and awaits elucidation by further observations relating clinical states with the mercuric chloride test.

REFERENCES

1. Race, J. (1935): *Rep. Chron. Rheum. Dis.*, **1,** 55.
2. Davis, J. S., Jr. (1936): *Journ. Lab. and Clin. Med.*, **21,** 478.
3. Scull, C. W., Bach, T. F., and Pemberton, R. (1939): *Ann. Int. Med.*, **12,** 1463.
4. Ropes, M. W., Rossmeisl, E., and Bauer, W. (1939): *Journ. Clin. Invest.*, **18,** 791.
5. Davison, R. (1940): *Journ. Lab. and Clin. Med.*, **25,** 935.
6. Collins, D. H., Gibson, H. J., Race, J., and Salt, H. B. (1939): *Ann. Rheum. Dis.*, **1,** 333.
7. Gibson, H. J., and Richardson, E. W. (1938): *Acta Rheumatologica*, **10,** 30.
8. Green, C. A., Thomson, S., and Glazebrook, A. J. (1939): *Ann. Rheum. Dis.*, **1,** 180.
9. Weltmann, O. (1930): *Med. Klin.*, **26,** 240.
10. Teufl, R. (1936): *Wiener Archiv. für Innere Med.*, **29,** 37, 297.
11. Hennes, H., and Kemen, A. (1936): *Klin. Wochenschrift*, **15,** 378.
12. Levinson, S. A., Klein, R. I., and Rosenblum, P. (1937): *Journ. Lab. and Clin. Med.*, **23,** 53.
13. Levinson, S. A., and Klein, R. I. (1938): *Amer. Rev. Tuberc.*, **37,** 200.
14. Levinson, S. A., and Klein, R. I. (1939): *Ann. Int. Med.*, **12,** 1948.
15. Klein, R. I., Levinson, S. A., and Rosenblum, P. (1940): *Amer. Journ. Dis. Child.*, **59,** 48.
16. Crane, M. P. (1934): *Amer. Journ. Med. Sci.*, **187,** 705.
17. Kirk, R. C. (1936): *Journ. Amer. Med. Assoc.*, **107,** 1354.
18. Bowman, R. O., and Bray, R. S. (1937): *Journ. Lab. and Clin. Med.*, **22,** 532.

19. CHASNOFF, J., AND SOLOMON, S. (1938): *Journ. Lab. and Clin. Med.*, **23**, 887, 894.

20. TARAN, A., AND LIPSTEIN, S. (1939): *Journ. Lab. and Clin. Med.*, **24**, 479.

OBSERVATIONS ON RHEUMATIC DISEASES UNDER WAR CONDITIONS*

BY OSWALD SAVAGE

SINCE the outbreak of the German air offensive against this country an opportunity has arisen to observe patients in the various stages of rheumatic diseases who have been living under active war conditions.

The intermittent bombing of London which for long spells has been of nightly occurrence has brought both mental and physical stress which would tend to cause the onset of rheumatic conditions in those susceptible and the aggravation of the symptoms of those already suffering.

The attendance at both clinics where I have worked has shown an increase during the last year despite the large evacuation from London and the fact that many of those requiring treatment have come irregularly owing to the difficulties of travel and the fear that the clinic might have been destroyed. The only decrease has been in the type of patient with rather vague rheumatic pains and no clinical abnormality who responded to many types of treatment for a time and then passed on to another clinic. These were usually of a nervous temperament and may have taken advantage of the evacuation schemes.

The feature most directly affecting the health of Londoners is the necessity of the nights spent in shelters. The two most detrimental elements are the shortage of sleep and the cold and damp often prevalent. Rheumatic subjects are particularly vulnerable.

I have questioned patients on the types of shelters they use and have seen representative examples.

In the suburbs the Anderson shelter is most common, and as these shelters are sunk into the ground it is impossible to exclude

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the damp. When water once enters these shelters it is extremely difficult to expel it.

In many parts of London where the houses have basements one in each street is appropriated, strengthened and inhabited communally. Though not as exposed as the Anderson shelters, there is a lingering humidity owing to the particular house and the surrounding dwellings often being empty because of evacuation.

The concrete turf-covered shelters constructed to accommodate 50 to 180 people are little used at night, as they are so cold and cramped.

Large public shelters, mostly in the East End, holding hundreds or even thousands, have been filled to capacity, as they are safe and there are few basements in that area. The conditions at the beginning of the Blitzkrieg were appalling. The occupants slept either on the damp stone floors, on a mattress which became saturated or in deck chairs. Added to this acute discomfort there was a complete lack of sanitation, a fœtid atmosphere and constant noise. Since the Horder Commission sweeping reforms have been carried out: sanitation installed, bunks constructed, first-aid posts established and damp areas walled off.

Tube shelters are probably the safest and driest of all. The atmosphere, however, is oppressive, and until recently there have not been enough bunks for all, so that people have had to sleep in unnatural positions.

Because of the vast national effort a large proportion of the population have changed to more rigorous occupations. Women have undertaken jobs usually done by men and many have taken up regular work for the first time, therefore bringing unaccustomed muscles into use. Increased production and A.R.P. duties have lengthened working hours and added an extra strain on physique.

I have seen examples of the various types of rheumatic disease and met one new condition. This is a bilateral painful œdema of the feet which has been termed "shelter feet." It is apparently the result of sleeping in a sitting position, often in a deck chair, with the knees flexed. The œdema and painful distension of the skin are secondary to impaired venous return.

The remaining cases have mainly fallen into the grouping of fibrositis, the rheumatoid type of arthritis and osteo-arthritis.

1. Fibrositis

This comprises the majority and may be divided into two groups: firstly, occupational, due to muscular strains; secondly, environmental, due to sleeping in cramped positions.

(*a*) *Occupational.*—The chief muscle groups affected have been those of the forearms and thighs, with the pains referred to the regions of the wrist and knee joints. On questioning, the patients relate that they have used either their arms with some unaccustomed tool or hand lathe, or their legs in driving a heavy vehicle, or a pedal to turn a machine.

On examination the pain has been reproduced by a particular opposed movement, and small areas of acute tenderness have been found, presumably where there has been a slight tear in the muscle. These cases have responded well to injection of local anæsthetic into the tender areas, followed by remedial exercises.

(*b*) *Environmental.*—Here the muscles most frequently involved have been the trapezii and glutei, the former from sitting for long periods with the shoulders leaning against a cold, damp wall, and the latter from sitting either on stone floors or saturated cushions.

In the case of trapezial involvement the pain was referred either up to the neck or occiput or down the arms, while in the latter the area of reference was down the back of the thigh, causing sciatica.

On examination there has been a diffuse tenderness on palpation of the muscle, but less pain on movement than in the previous group. A number of nodules were occasionally found, but single areas of exquisite tenderness on palpation have been rare.

Treatment of these cases is more difficult, but in general they have responded steadily to heat followed either by massage or to ionisation with histamine.

I noted that in both types of fibrositis the blood sedimentation rate (Westergren) has been normal.

2. The Rheumatoid Type of Arthritis

It is a clinical assumption that many factors play a part in the ætiology of the rheumatoid type of arthritis. So many patients attribute the onset to some emotional upset that there

is evidently a large psychological element in the production of this disease. The present disturbed conditions caused by air attacks on London would therefore tend to result in the increase of rheumatoid arthritis both from fresh cases and from relapses.

It is too early to be certain whether this has occurred, but the indication that at both clinics the number of cases of the rheumatoid type of arthritis has increased while the population of London has diminished would point to this probability being a fact.

I have questioned patients as to what they attributed their onset or relapse, and in a large number of cases they have replied that it was due to bombing, either being bombed themselves or the loss of a relative or friend. "You see, it was the shock that brought it on," was a common answer.

The psychological state of these patients has also sometimes reacted in their favour, for the excitement of doing dangerous work and being kept on the alert has in many cases resulted in a steady improvement in their general and local condition. Many of the patients, noticeably the women, have been employed on A.R.P. duties such as ambulance drivers or wardens, working long hours and in key positions. It has been striking how they have been able to keep at their work through an arduous winter, often having no time to come to the clinic other than for the weekly injection of gold. They say that they feel better and show an increase in weight and an improvement in the joint movements, together with a fall in sedimentation rate. In fact, some have expressed surprise that they have managed so well. This improvement may, of course, be due entirely to the gold salt therapy, but I believe the fact that they are doing an essential national service has been a helpful stimulus.

A certain number of patients suffering from rheumatoid arthritis require hospital treatment at some period. Their health deteriorates and they lose weight so rapidly that in spite of supervision and treatment as out-patients they are unable to carry on. Under the stress of war this point seems to be reached more rapidly than in time of peace, and I have found that whereas formerly many patients were reluctant to submit to hospital treatment and would struggle on, sometimes for months, they are now only too willing to be admitted within a few weeks of the onset.

Another probable factor in the causation of rheumatoid

arthritis is focal infection. Luckily there has not been the increase in such infections that was expected, so there has been no opportunity to study this.

3. Osteo-arthritis

Patients suffering from this degenerative condition have fared badly in London during the winter. Many of them had been enabled to keep about and their pain had been controlled by repeated courses of physiotherapy at hospitals and clinics. These they required more especially in the winter months.

As a result of the war some clinics have had to close for periods and staffs have been depleted. In addition, travel to treatment centres, always a problem for these patients, has become even more difficult. In consequence they have suffered more than any other group.

Conclusion

Rheumatic sufferers as a class are often accused of being difficult patients to treat because they are of a nervy temperament.

It has been noticeable how they have vindicated themselves during the past critical months, often being bombed out of their homes and having to work longer hours than formerly. They have accepted treatment gratefully and kept on cheerfully at their work, often rather to their own surprise, and have certainly played their part in the national effort.

It would appear that there has been an increase in rheumatism, at any rate in London, and that there will be greater numbers requiring treatment. With the vast improvements in shelter conditions their lot may be alleviated, but it is essential that clinics for advice should be kept going to aid them.

OBSERVATIONS ON RESPIRATION IN ARTICULAR CARTILAGE*

By MORRIS A. BOWIE, OTTO ROSENTHAL and GEORGE WAGONER

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Little was known about the metabolism of articular cartilage till 1936, when Bywaters[1] published the first quantitative data on the subject. He reported a well-defined glucolysis, equivalent per cell to that of other adult tissues, but was unable to demonstrate an appreciable utilization of oxygen. It seemed improbable that a tissue without any respiratory ability could synthesise the complex constituents of its matrix. Since Bywaters had employed old equine cartilage in his study, reinvestigation of the problem, using cartilage of young as well as of older animals, seemed worth while. Accordingly, bovine articular cartilage secured from young, adult, and old animals was employed.

The Respiratory Power of Cartilage Cells in Different Ages

The comparison of the respiratory power of articular cartilage cells at different ages was based on the manometric determination of the oxygen uptake of surviving cartilage slices in a substrate-free phosphate Ringer's solution. Use of the rate of spontaneous oxygen consumption (auto-respiration) as a measure of the respiratory power of cartilage appeared justifiable because of two observations: (1) The constancy of auto-respiration over extended experimental periods indicated that its rate was not limited by a lack of combustible substrates; and (2) the addition of substrates either did not significantly increase or did depress the rate of auto-respiration.

In order to evaluate the respiratory power of cartilage cells at different ages from the measured rate of oxygen uptake per unit

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mass of slices, allowance had to be made for the decrease in the cell content of the slices with ageing. It was shown by means of cell counts[2,6] that the rate of anaerobic glucolysis, which is readily demonstrable manometrically, was proportional to the cell content of the slices in all the ages studied. Hence, the ratio

$$\frac{\text{(rate of auto-respiration)}}{\text{(rate of anaerobic glucolysis)}} \times 100$$

could be used as an estimate of the respiratory power of the cartilage cells.

The ratio of auto-respiration to glucolysis amounted to 8 : 1 in calves under half a year of age to 5 : 7 in adult animals one to seven years old and to 3 : 1 in animals eight years and older. The differences between the mean ratios obtained in the three age groups were statistically significant.

The ratio of auto-respiration to glucolysis in old bovine articular cartilage was in close agreement with Bywaters' data for equine material. The ratio in calf cartilage, however, was two and a half times greater than Bywaters' figure. Thus, our experimental data indicated that young cartilage cells were endowed with a small, but well-defined respiratory power in addition to their glycolytic capability. In contrast to the glycolytic power, however, the respiratory power of the cartilage cell decreased by 60 per cent. during the process of maturation and ageing.

The Properties of Respiration in Calves' Cartilage

The data of Table I indicate that the respiratory quotient of calves' cartilage in a substrate-free medium was compatible with the combustion of either protein and fat or of carbohydrate and fat. Bywaters obtained an R.Q. of 0·71 for synovial membrane, suggesting oxidation of fat alone.

A peculiarity of cartilage respiration consisted in the marked depressing action which glucose exerted upon the respiratory rate. We suggested[3] as one possible explanation that the utilization of the added glucose by cartilage cells prevented the combustion of certain cellular substrates. Particularly, cellular protein might be conserved since the protein-sparing action of glucose has long been recognised.

Because of the high aerobic glucolysis in articular cartilage it seemed evident that a glycolytic utilization of glucose might be

responsible for the depressing action of this hexose on respiration. However, the significant increment of the R.Q. by the addition of glucose to cartilage (*cf.* Table I) demonstrated that an oxidative utilization of the hexose took place simultaneously with its glycolytic breakdown.

The results of experiments summarised in Table II showed that the addition of iodoacetate in a concentration that inhibited glucolysis by about 95 per cent. virtually abolished the depressing action of glucose on the respiratory rate. This effect of iodoacetate strongly suggested that the depressing action of glucose on cartilage respiration was linked with the glycolytic splitting of the hexose.

In order to secure more information on the type of combustions which were started after the blocking of glycosis, we determined the R.Q. of cartilage slices in the presence of iodoacetate. Table II shows that under these conditions the R.Q. still remained close to one. This order of magnitude of the R.Q. values demonstrated that fat combustion did not play an essential rôle in articular cartilage even if carbohydrate utilisation had been greatly limited. The values were compatible with the oxidation of protein to water, carbon dioxide, and ammonia, a process which could produce R.Q. values of 0·95. This interpretation is to be regarded as tentative, since the ammonia metabolism of the cartilage cell was not studied.

At present it cannot be excluded that respiration in the presence of iodoacetate was based upon the oxidation of small amounts of lactic acid which were either preformed or produced by the cells in spite of the presence of the drug. The persistence of only 3 per cent. of the glycolysis would be sufficient to yield the amount of lactic acid required for the respiration observed.

An oxidation of lactic acid by articular cartilage was indicated by the fact that the addition of lactate increased the rate of respiration if the new formation of lactic acid from cellular carbohydrate was restricted by the presence of iodoacetate. Indications for the oxidations of pyruvic and succinic acids have been previously reported.[3]

The experimental results discussed above justify the conclusion that the young cartilage cell is capable of completely oxidising carbohydrate and, possibly, protein.

Dehydrogenase Systems in Articular Cartilage

Bywaters in 1936[1] noted that the addition of methylene blue to equine articular cartilage markedly increased the rate of oxygen consumption. He pointed out that articular cartilage was apparently endowed with dehydrogenatic enzymes, but that the function of this substrate-activating group of the respiratory enzymes in a tissue devoid of respiratory power remained a mystery.

The intensity of the dye-stimulated respiration in bovine articular cartilage facilitated a more detailed study on the nature of the dehydrogenatic processes. The R.Q. of the dye-stimulated respiration ($0{\cdot}865 \pm 0{\cdot}027$) had an order of magnitude similar to that of the auto-respiration of calves' cartilage.[4] The rate of the dye-stimulated respiration was slightly but definitely increased by the addition of lactate or pyruvate and sustained by the addition of succinate. Thus, the reactions which were accomplished by the joint action of the cellular dehydrogenases and the artificial oxidation-reduction dye had the same character as the natural cartilage respiration, where the oxygen-activating group of the respiratory enzymes took the place of the experimental redox dye. This qualitative similarity between the dye-stimulated and the spontaneous respirations demonstrated directly the function of the dehydrogenases in cartilage metabolism.

In contrast to the spontaneous respiration of articular cartilage the dye-stimulated respiration was markedly increased by the addition of glucose. Like the depressing effect of glucose on the spontaneous respiration, the accelerating action of the hexose on the dye-stimulated respiration was completely abolished when glucolysis was inhibited by iodoacetate.

It is known that the transformation of triose-phosphate to phosphoglycerate—the oxidative step of the glycolytic oxidation-reduction of glucose to lactic acid—is an enzymatic reaction which is especially sensitive to iodoacetate poisoning. In view of the equally great sensitivity to iodoacetate of both the anaerobic and the aerobic glucose utilization in articular cartilage it seemed highly probable that the system triose-phosphate dehydrogenase+co-enzyme 1 participated in the normal glucose respiration as well as in the oxidation of glucose by methylene blue. It is possible that at this point of the intermediary glucose

metabolism the glucolytic and oxidative pathways diverged. The subsequent stages of the glucose oxidation by methylene blue, a combustion which was apparently not complete,[4, 5] remain to be studied.

Thus far analysis of the nature of the dye-stimulated respiration in articular cartilage has provided indications that dehydrogenase systems concerned with the oxidation of glucose, lactate, pyruvate, and succinate are present. Since all of these substances were metabolised by calves' cartilage in the absence of dye, the rôle of dehydrogenatic enzymes in the metabolism of articular cartilage appears understandable.

Dehydrogenatic Power of Cartilage Cells in Different Ages

The decline of the respiratory power of ageing cartilage cells raised the question as to whether the whole or only one group of the respiratory enzymes diminished in amount with the progress of age. Changes in the amount of dehydrogenases—*i.e.*, in the substrate-activating group of respiratory enzymes—were most suitable for a quantitative estimate, since the rate of the dye-stimulated respiration provided a measure of the dehydrogenatic capacity of cartilage in the different ages.

The addition of methylene blue to surviving slices of cartilage increased the initial rate of oxygen consumption three-fold in calves, ten-fold in adult animals, and twenty-fold in old animals. The extent of the stimulative effect of methylene blue in the age groups showed that only a fraction of the total dehydrogenatic capacity of the cells was utilized in normal respiration and that this utilized fraction diminished in ageing cells. Because of this excess of dehydrogenatic capacity over total respiratory capacity in all the ages studied, it seemed likely that the declining respiratory power of the ageing cells was due to a deterioration of their oxygen-activating power.

For a quantitative comparison of the dehydrogenatic power in the age groups the rate of the dye-stimulated respiration in a substrate-free medium was of limited value, because changes of the rate incident to ageing might depend not only upon differences in the enzyme content of the tissue, but also upon variations in the amount of cellular substrates. It seemed more accurate, therefore, to restrict the comparison to one single dehydrogenatic process, such as glucose dehydrogenation, where the substrate

concentration could be kept under experimental control. The increment of the rate of the dye-stimulated respiration due to the addition of glucose was employed as a measure of the rate of glucose dehydrogenation. The ratio of this increment to the rate of anaerobic glycolysis served as an estimate of the glucose-dehydrogenatic power per cell.[6]

The ratio of glucose dehydrogenation to glucolysis increased by 11 per cent. from infancy to adolescence and decreased by 23 per cent. from infancy to old age. The changes of the ratio with age were, however, not statistically significant.

This result lent support to the view that the dehydrogenatic power of the cartilage cell changed very little, if at all, during the process of ageing. Thus, it seemed highly probable that the deterioration of the respiratory power in ageing articular cartilage could be ascribed to a gradual loss of components of the oxygen-activating group of the respiratory enzymes.

The Inter-relationship of Degeneration, Ageing, and Metabolic Activity

Bauer and Bennett have shown that alterations in articular cartilage, characteristic of degenerative or hypertrophic arthritis, occur in all cattle over two years of age.[7] In young adult cattle the degenerative changes consist in circumscribed lesions on the proximal surfaces of the metacarpals. With advancing age, additional joints become affected and general degenerative alterations in cells and matrix accompany the localised defects The decline in the respiratory power of articular cartilage was recognizable at the same age period when the first arthritic phenomena became apparent and the decline progressed with the extension of the degenerative alterations.

The diminution in the respiratory power of articular cartilage should not be considered a consequence of the degenerative alterations, because it is found in the cartilage from joints where both macroscopic and microscopic alterations are still absent. Obviously, the loss in metabolic activity is correlated with the chronological and structural age of the cartilage, and precedes the visible manifestations of the process of ageing. The gradual decline of the respiratory power might be denoted as the metabolic equivalent of the process of ageing in articular cartilage. In view of the fact that degenerative arthritis (hypertrophic or osteo-arthritis) is a disease of the more advanced age groups in

man, the gradual loss in the respiratory power of articular cartilage is possibly an intrinsic factor in the development of degenerative arthritis.

Conclusions

Articular cartilage of calves exhibits a small but well-defined respiratory activity. The young cartilage cell is capable of oxidising carbohydrate and, perhaps, protein.

The respiratory power of bovine articular cartilage cells decreases by 30 per cent. from infancy to adolescence and by 60 per cent. from infancy to old age. This decrease is probably due to a gradual loss of components of the oxygen-activating group of the respiratory enzymes, because the activity of the dehydrogenatic group of these enzymes remained virtually constant throughout the age groups tested.

In view of the parallelism between the decrease of respiratory power and the appearance of degenerative alterations in ageing bovine cartilage it is suggested that a gradual loss of the respiratory power of the cartilage contributes to the higher frequency of degenerative joint diseases in the more advanced age groups of man.

It remains for further study to find out if and how the cartilage cell utilizes its respiratory capability for the synthesis of specific constituents of cartilage tissue, and to elucidate the nature of the enzymatic components which diminish in amount with the progress of age.

Table I.—The Influence of Glucose upon the Respiratory Rate and upon the Respiratory Quotient of Calves' Cartilage.

Gas: Air. Medium: Phosphate Ringer's. pH: 7·4. Respiratory rate: 1μ O_2 consumed per mg. dry weight of cartilage per hour. Experimental period: Three hours for the determination of rates, four hours for R.Q. measurements.

	Respiratory Rate.		*Respiratory Quotient.*	
	No Addition.	*M/100 Glucose.*	*No Addition.*	*M/100 Glucose.*
Number of experiments	37	25	22	14
Mean values	0·096	0·044	0·907	1·033
Standard error	±0·0027	±0·0172	±0·0099	±0·0370
Change of Means due to glucose	− 0·052 ±0·0032		+0·126±0·0398	

TABLE II.—ACTION OF IODOACETATE ON CARTILAGE RESPIRATION. Experimental period: Four hours.

Additions.			+ *M*/10,000 *Iodoacetate.*			
					M/100 *Glucose.*	
	Rate.	*R.Q.*	*Rate.*	*R.Q.*	*Rate.*	*R.Q.*
Number of experiments	10	8	10	8	10	10
Mean values	0·095	0·886	0·094	0·959	0·090	0·991
Standard error	± 0·0038	± 0·0217	± 0·0045	± 0·0213	± 0·0036	± 0·0149

REFERENCES

1. BYWATERS, E. G. L.: "Reports on Chronic Rheumatic Diseases," 1936, No. 2, 104.
2. ROSENTHAL, O., BOWIE, M. A., AND WAGONER, G.: *Journ. Cell. and Comp. Physiol.*, 1941, xvii. 221.
3. ROSENTHAL, O., BOWIE, M. A., AND WAGONER, G.: *Science*, 1940, xcii. 382.
4. ROSENTHAL, O., BOWIE, M. A., AND WAGONER, G.: *Journ. Cell. and Comp. Physiol.*, in preparation, 1940.
5. HILLS, G. M.: *Biochem. Journ.*, 1940, xxxiv. 1070.
6. WAGONER, G., ROSENTHAL, O., AND BOWIE, M. A.: *Amer. Journ. Med. Sci.*, 1941, cci. 489.
7. BAUER, W., AND BENNETT, G. A.: *Journ. Bone and Joint Surg.*, 1936, xviii. 1.

REVIEW

RHEUMATISM. A PLAN FOR NATIONAL ACTION. Lord Horder. H. K. Lewis and Co., 2s.

Lord Horder has written this book as Chairman of the Empire Rheumatism Council. In it he attempts the difficult task of making himself intelligible both to the profession and the lay public and succeeds well.

The broadest definition of rheumatism is accepted, and not only are rheumatic fever and arthritis in its various forms included, but non-articular rheumatism—fibrositis, neuritis, sciatica, lumbago, bursitis, etc.—is also considered.

It is estimated that the number of sufferers from rheumatic disease in England and Wales is not less than a million adults and 200,000 children. Vast as the figures are, I believe them to be, if anything, an under-estimate. A few years ago I had occasion to visit every house in a certain district of a large provincial town. I was astonished to find the number of chronic invalids of all ages that were to be found in almost every street, and even more surprised to discover that by far the commonest cause of invalidity was rheumatic disease.

The chapter on the etiology of rheumatism is a good one. The importance of occupation, climate and focal sepsis are all stressed, as well as the need for a reasonable standard of comfort in the home, especially in the case of children. An investigation is quoted that indicates that acute rheumatism is three times as common in children coming from poor homes as in children of the same social class living in well-managed children's institutes.

The next chapter sets out fairly and squarely what can be expected from the treatment of rheumatic disease and the point is repeatedly stressed that the one thing necessary above all else is early and correct diagnosis. It is suggested that the various types of treatment can be divided into two classes: (1) the ordinary, which can be carried out in any clinic—mainly physical but to a less extent medical; and (2) the more unusual, which require special technique and experience for their application, or which are still on trial and have not yet been generally accepted.

The third chapter is the most important; it is the one that gives the book its essential value; it is a plan for national treatment. It is, of course, a bold man who is prepared to propound a scheme for the treatment of a disease the etiology of which is so obscure. But the scheme is here and it seems reasonable and workable. Its author realises two important facts: firstly, that prevention, treatment, research and education of the medical profession are both essential and intimately associated; and, secondly, that no scheme can be efficient that does not include the doctor who first sees the patient and has to make the first diagnosis, however provisional it may have to be.

The plan for national treatment is divided into two sections: (1) for children and (2) for adults. In connection with the former a high tribute is paid to the L.C.C., whose scheme "can be said to be the best existing to-day in any quarter of the world." The first essential of this scheme is a complete medical examination of every scholar at least four times during school life, together with re-examinations and special examinations whenever there is the slightest indication of the desirability of either. The pivot on which the whole L.C.C. scheme hinges is the Rheumatism Supervisory Centre. To these centres are referred—(*a*) children with a history of acute or sub-acute rheumatism or chorea; (*b*) children having symptoms (such as muscular pain) suggestive of a mild rheumatic infection; (*c*) suspected cases for diagnosis. The centres act as clearing-houses and from them cases are referred for treatment. Those requiring in-patient treatment are sent for the most part to the five Rheumatism Units containing in all about a thousand beds and situated well away from the smoky area of central London. Children continue their education while in hospital, and the keenness and kindliness of the teachers in these hospital-schools is beyond all praise. Some children are able to return to an ordinary school when they leave hospital, but a good many have to attend a school for physically defective children, to which they are conveyed daily from their homes by motor ambulance. In all cases there is thorough after-care supervision. The scheme is admittedly an expensive one, and it is not too easy to estimate correctly the value of the results obtained. We know, however, that rheumatism is the principal cause of heart troubles in children and that the incidence of heart disease in L.C.C. school children has fallen from 2 to 0·77 per cent. between 1926 and 1937. Lord

Horder is full of praise for this scheme. He would like to see similar schemes applied to all children in all areas. His only suggestion for improvement is "that there should be a sustained effort to raise the standard of knowledge in regard to rheumatic disease of the school medical officers in order to reduce to the lowest possible degree the chance of early indications being overlooked."

The proposed scheme for adults is heralded by the astounding statement (which I believe to be only too true) that it is probable that less than 10 per cent. of sufferers from rheumatism obtain the special treatment necessary in the early stages. The scheme for adults follows closely on that for children. There are to be a relatively few Specialised Rheumatism Treatment Centres where everything necessary for diagnosis and for all forms of treatment will be at hand, and where research can be carried out and new methods tried under accurate observation. Hospital beds must obviously be provided for these centres, and I would put in a plea for their close association with a large general hospital whenever possible, so that the necessary pathological and specialist services may be readily available. It is suggested that these Specialised Treatment Centres should also have important educational functions, teaching patients where necessary self-help and "home therapy" and giving post-graduate instruction to general practitioners in the early recognition of rheumatic disease and the simpler methods of treatment. Under the direct supervision of these Specialised Centres would be Local Treatment Centres. These should be for out-patients only and much more numerous. There should be a Medical Supervisor and full staff for the simpler methods of physical treatment. Patients would be sent on by their local doctor and would remain under his care for everything except special rheumatism therapy.

The last chapter is on finance. I have no space left to deal with it, and perhaps it is just as well, for it is less clear and definite than the rest of the book and by no means easy to summarise in a few words.

The plan for the national treatment of rheumatic disease is a good one. The thoughtful reader may be pardoned if he enquires whether a similar plan might not usefully be adopted for the treatment of many other diseases, or perhaps indeed of all.

SOMERVILLE HASTINGS.

THE EMPIRE RHEUMATISM COUNCIL

Six Months' Progress

Developments during the past half-year amply justified the courageous decision of the Empire Rheumatism Council to carry on with its work despite the outbreak of war. There has been very encouraging progress.

Particularly gratifying has been the manifestation of warm American sympathy with our work. The following are extracts from letters received:

Dr. Homer F. Swift (Hospital of the Rockefeller Institute for Medical Research): "I am in receipt of the Fourth Annual Report of the Empire Rheumatism Council, which was so kindly sent me by Lord Horder and the Council, and I have read it with very great interest. May I congratulate you on the manner in which you are adapting your particular problems to those imposed by the war, for in this way the objectives of your Council will not be entirely lost sight of. In fact, the flexibility is something that we can all emulate."

Dr. Loring T. Swaim (American Rheumatism Association): "This is one of the most stimulating defence reports I have heard about, and I certainly congratulate you on the way you carry on. Congratulations and the very best of luck."

Dr. D. H. Kling: "I wish to express my appreciation of the report of the Empire Rheumatism Council. I am doing my best to acquaint my colleagues and the associations of which I am a member with the truly remarkable work which you are carrying out under these trying circumstances."

Mrs. Edwin H. Koehler (First Vice-President, Irvington House): "We were most encouraged upon receipt of your report. Your bravery and courage have aroused our profound admiration. We send you our sincere hopes for the attainment of that which we all desire."

At the request of Dr. Swaim, copies of the report were posted to the chief rheumatologists in the U.S.A., and fifty copies were sent to him in bulk for circulation to lay members of the American Rheumatism Association.

It is proposed to invite a representative American rheumatologist to join the Editorial Board of our official Journal.

Obviously the burden of the " war on rheumatism " will fall in the future chiefly upon scientists of the U.S.A. and of the British Empire, since the enemy is systematically uprooting all humanitarian effort in Europe. Therefore the cultivation of the closest relations with American science is the right policy for our Council.

A welcome letter reached Lord Horder in April from Dr. R. B. Osgood, stating that the medical profession of Massachusetts, U.S.A., contemplated the establishment of a Specialised Rheumatism Hospital. The scheme outlined followed exactly that consistently advocated by the Empire Rheumatism Council—viz., association with a great teaching hospital and assurance of the co-operation of its consulting staff. Lord Horder, as Chairman of the Empire Rheumatism Council, was asked to become one of the sponsors of this scheme, and agreed. There have been communicated to Massachusetts full particulars of our Council's work, with assurances of all possible assistance to their scheme. Recognition from scientific bodies in America of the international value of our work is greatly appreciated.

The Council's Research Work

The terms of engagement of the staff of the Naval Research Foundation have been extended for one year until the middle of 1942.

Dr. Dyson, with his collaborator, Dr. Margaret Green, have begun their research work in the North with the equipment transferred from the Maclean Laboratory at the Hospital of St. John and St. Elizabeth.

The Plan for National Action

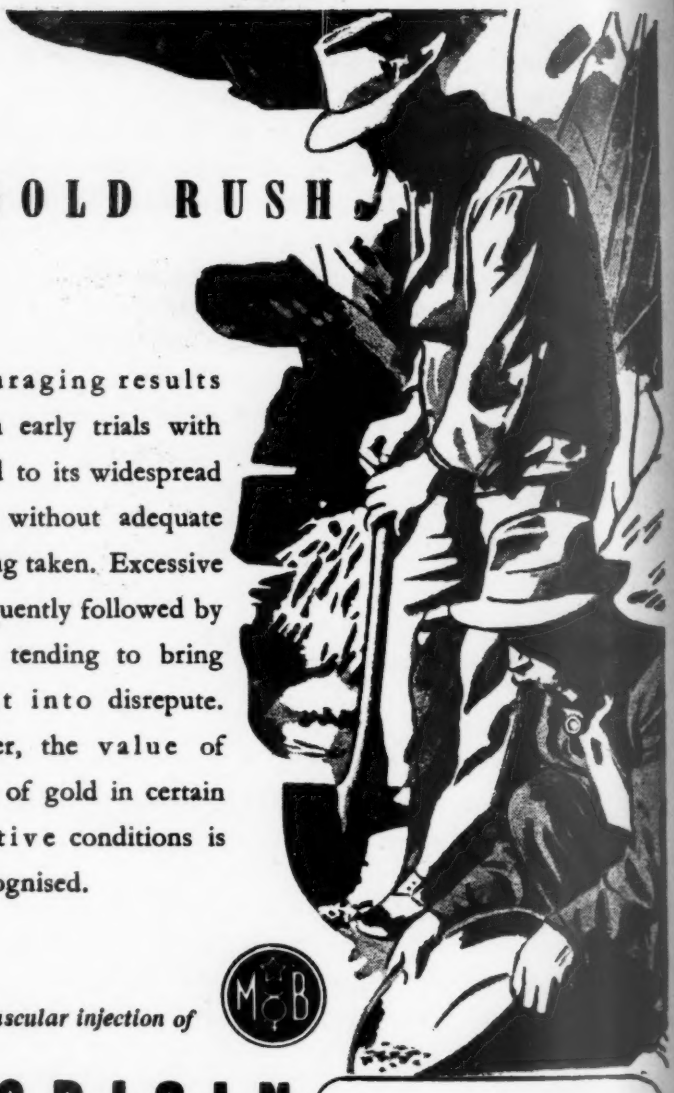
This book by Lord Horder in collaboration with the Empire Rheumatism Council was published March 26. It had a notable welcome from the Press, medical and lay. The first edition (3,000 copies) was quickly taken up. The second edition was ordered April 4 (1,000 copies). Demand was developing so well that on April 21 the printing order for this edition was extended to 2,000 copies. These were ready on Apri' 25. There remained on hand on April 31 about 500 copies. Industrial organisations are now being approached to promote the circulation of the book

among their welfare workers. Effort is not being neglected to increase demand from retail booksellers. A third edition probably will be needed in the near future.

What is more important is that the book has stirred local communities to thought of action. From three centres (in England, Scotland and Northern Ireland) letters have come indicating an effort to set up treatment centres, and seeking the advice of our Council. There is no doubt that the publication is assisting greatly the " war on rheumatism."

Administration

Col. F. D. Howitt, C.V.O., F.R.C.P., and Mr. Gordon Thompson, F.R.C.S., have been co-opted to the War Emergency Committee of the Council.



THE GOLD RUSH

THE encouraging results obtained in early trials with gold therapy led to its widespread use, frequently without adequate precautions being taken. Excessive dosage was frequently followed by toxic reactions tending to bring the treatment into disrepute. Today, however, the value of small quantities of gold in certain chronic infective conditions is universally recognised.

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